TUMORS of the UPPER RESPIRATORY TRACT and EAR

by

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and

LESLIE MICHAELS, M.D.

AFIP

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ATLAS OF TUMOR PATHOLOGY

Second Series
Fascicle 25

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EDITORS' NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences—National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was done by the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 Fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final Fascicle of the first Atlas, the National Academy of Sciences—National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this series, the terminology chosen for the World Health Organization's series "International Histological Classification of Tumours" will be used when available. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information when indicated for a better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index is included in each Fascicle.

It is the hope of the Editors, past and present, the Editorial Advisory Committees, past and present, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will always be appreciated.

William H. Hartmann, M.D.
Leslie H. Sobin, M.D.

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PREFACE AND ACKNOWLEDGMENTS

The Fascicle is intended to present as inclusively as possible the pathology of tumors that involve the sinonasal tract, pharynx, larynx, trachea, and temporal bone, the latter to include the ear. These anatomic areas in days gone past were the regions of medical interest to the otolaryngologists. However, today these same practitioners have become clinically involved in other areas of the head and neck, such as the neck, thyroid, major salivary glands, oral cavity, and facial cosmetics. The tumors of these latter regions, including the faucial and lingual tonsils, are adequately presented in other Fascicles.

This Fascicle is designed for use by the clinician and pathologist, both the student and experienced. The clinical aspects of the tumors are generously discussed, together with the pathology and current therapy.

The classification and definitions of tumors of the upper respiratory tract and ear are those essentially advocated and sponsored by the World Health Organization (WHO) and we are indebted to Dr. Leslie H. Sobin of the Armed Forces Institute of Pathology (AFIP) and to WHO for their encouragement and permission to utilize this information and expertise.

We are particularly appreciative of all the contributors of material through the years to AFIP, without whom there would be no Fascicle. When contributors of particular cases are known, we have attempted to acknowledge their contributions and we apologize if we have neglected to recognize anyone's generosity, due to our oversight. Dr. Frank King, Chairman of the Lymphatic and Hematologic Pathology Department, and Captain Dennis Heffner, MC USN, Chairman of the Otolaryngic Pathology Department, AFIP, were most generous in providing both advice and photographs for the Fascicle.

This Second Series of the Atlas of Tumors of the Upper Respiratory Tract and Ear is a follow-up to the First Series Atlas of the same name that was authored so expertly by the late Colonel James E. Ash, MC USA (Ret.), and his co-writers Colonel Marcus R. Beck, MC USA (Ret.), and J. Daniel Wilkes, M.D. This original work was indeed an inspiration and a guide to the present edition and we are grateful to Colonel Ash and his co-authors for their influence.

There are so many other people who contribute to a production such as this and do not receive deserved acknowledgment. However, the artwork contained herein must be recognized and an expression of appreciation given to Elisabeth McDonnell of the AFIP Scientific Illustration Division. The hundreds of photographs that compose this Fascicle are possible due to the dedication of Mr. J.J. Durek, Jr., and his skillful associates from the Department of General Photography of the AFIP.

Vincent J. Hyams, Captain, MC USN (Ret.)
John G. Batsakis, M.D.
Leslie Michaels, M.D.

TUMORS OF THE UPPER RESPIRATORY TRACT AND EAR

Contents

TUMORS OF THE UPPER RESPIRATORY TRACT

INTRODUCTION

Color Plates I and II present the general anatomy of the upper respiratory tract with the essential features appropriately labeled. These anatomic presentations may be utilized in augmenting the following discussion of the histology of the upper respiratory tract.

HISTOLOGY

Nasal Cavity

The vestibule or anterior chamber of the nasal cavity is an internal extension of the integument of the external nose, including a keratinizing, stratified, squamous epithelial surface and an underlying stroma of the fibrofatty tissue containing hair follicles, sebaceous glands, and sweat glands (fig. 1). The posterior extension of the vestibule may vary with physiologic conditions or racial and individual anatomic characteristics, but the average depth is between 1 and 2 cm from the external rim of the nares. As the mucocutaneous junction (limen nasi) representing the anterior limits of the inner nasal cavity proper is approached, there is a gradual diminution and disappearance of the submucosal

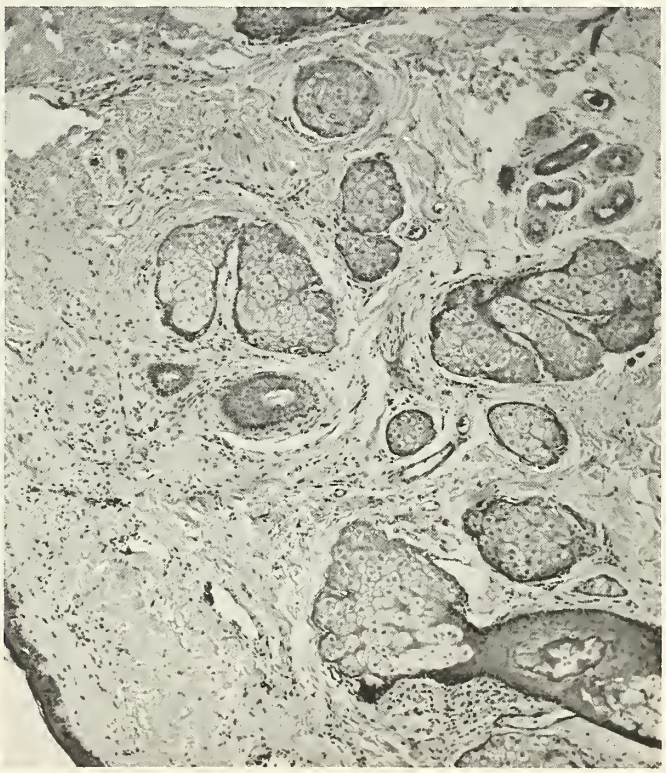
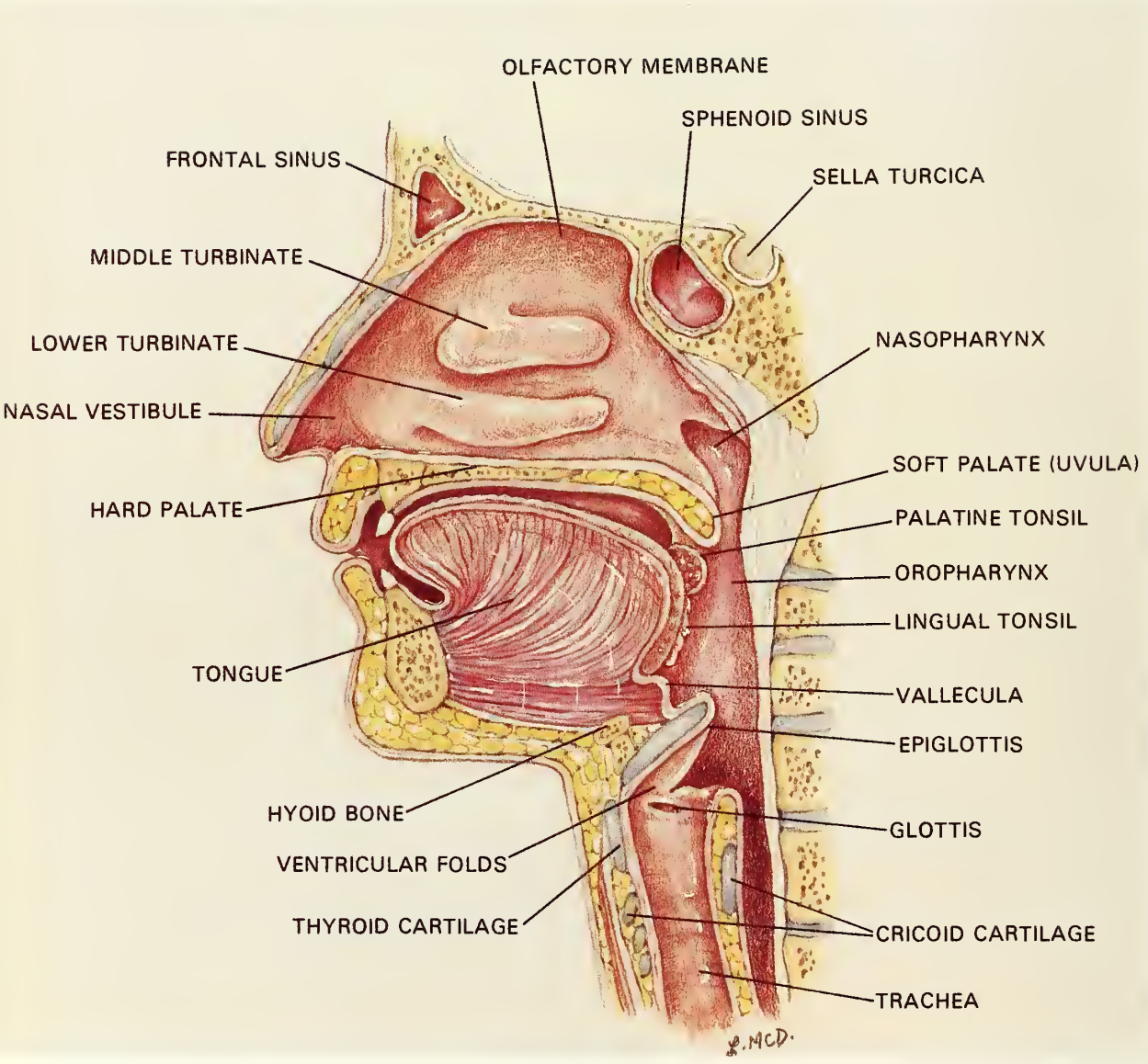


Figure 1
NASAL CAVITY
The histology of the nasal vestibule is essentially that of the skin surface, with the epidermis, dermis, and prominent adnexa (sebaceous glands, sweat glands, and hair follicles). X63.*

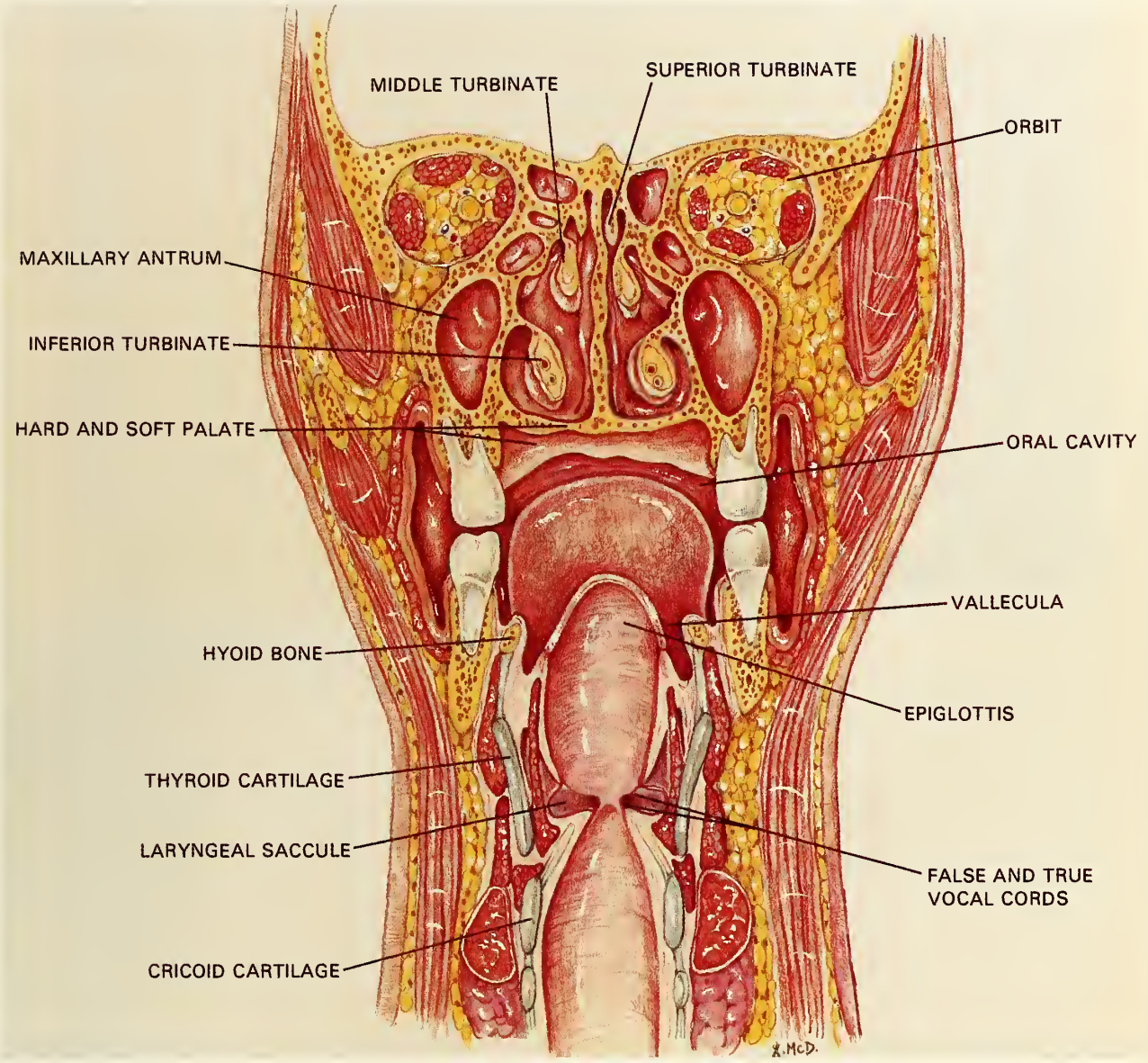
*Throughout the Fascicle where the stain is not designated, the hematoxylin and eosin stain has been used.

PLATE I



A SAGITTAL VIEW OF THE ANATOMY OF THE UPPER RESPIRATORY AND ORAL TRACT

PLATE II



A CORONAL VIEW OF THE SINONASAL TRACT, ORAL CAVITY, AND LARYNX

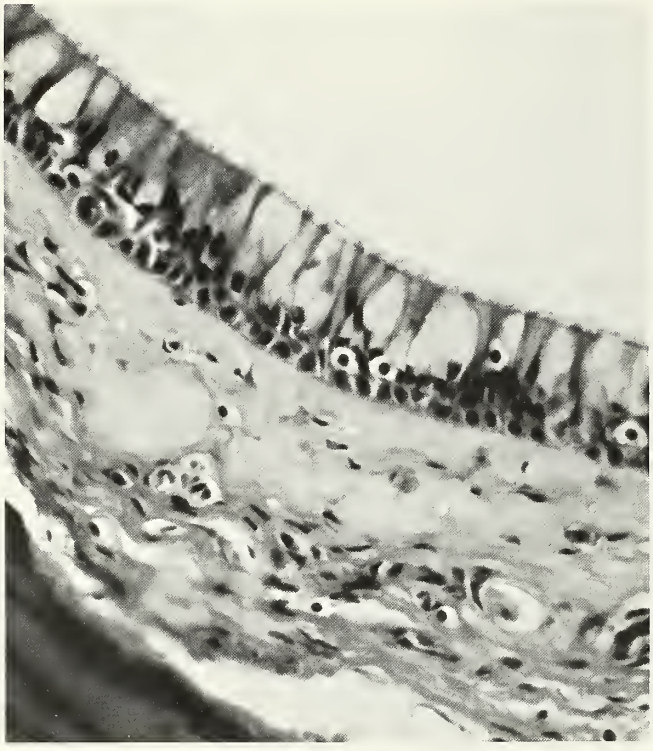


Figure 2
NASAL CAVITY
This illustration emphasizes the ciliated, pseudostratified, columnar (respiratory) mucosa characteristic of the sinonasal tract proper. X400.

adnexa. The sinonasal cavities are normally lined by a ciliated, pseudostratified, columnar epithelium (fig. 2), designated as the schneiderian membrane to emphasize its origin from the ectoderm as contrasted with similar appearing epithelium of the nasopharynx, larynx, and lower respiratory tract, which is of endodermal origin. The submucosa of the nasal cavity varies in thickness, being most pronounced over the inferior, medial, and lateral portions of the middle and lower turbinates (fig. 3), which represent the nasal surface most prominently exposed to inspired air. Immediately beneath the nasal cavity mucosa is a thin uniform zone of fibroelastic tissue, the lamina propria. Varying with location, the remaining nasal cavity submucosa may contain admixtures of mucoserous glands and distinctive vascular structures, the glandular elements being generally oriented nearer the surface. The majority of the vascular components, the vasae erecti, are similar in histologic structure to those forming the erectile tissue of the penis and clitoris and are capable of marked variation in luminal capacity. The pathologist may mistake this normal vascular pattern for neoplasia such as hemangioma or angiofibroma. The paranasal sinus submucosa may contain a few scattered mucoserous glands, particularly in the ostial area, but no prominent vascular network is noted, the usual normal finding being only a thin, submucosal, fibrous layer adjacent to the periosteum (Toppozada and Talaat).

The olfactory epithelium is normally found in the superoposterior portion of each nasal

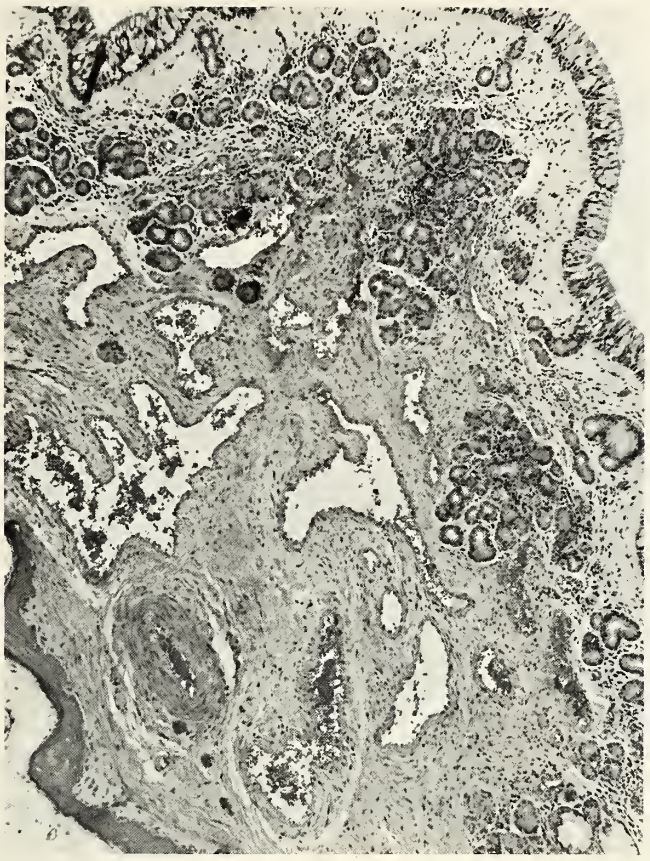


Figure 3
NASAL CAVITY
This shows the thickened areas of nasal cavity turbinates, caused by outer submucosal collections of mucoserous glands, and the inner submucosal vascular structures designated as so-called vasoerecti. X63.

cavity (fig. 4), occupying an area equivalent to a U.S. one-cent piece (Anson), and occasional patches may also be found on areas of the turbinates. The possible ectopic migration of portions of the olfactory placode into the maxillary sinus cavity is supported by figure 5. Grossly, this sensory zone reveals a yellow hue and is less vascular than the surrounding nasal mucosa. Histologically, it consists of an epithelium composed of elongated sustentacular (supporting) cells, small basal cells, and olfactory neural cells (figs. 6, 7). The last mentioned are bipolar, spindle-shaped cells with thicker peripheral processes which protrude from the mucosal surface, forming olfactory vesicles with their cilia-like structures projecting into an overlying mucus blanket. The proximal processes traverse internally toward the brain via the cribriform plate as nonmyelinated fibers synapsing within the olfactory bulb. Small serous-like Bowman's glands are located in the submucosa and their ducts open onto the olfactory mucosal surface. The columnar sustentacular cells resting on the basilar membrane have crowded microvilli on their surface facing the mucus blanket. A single layer of inner, mostly polygonal, basal cells perform as reserve cells for the replacement of sustentacular cells.

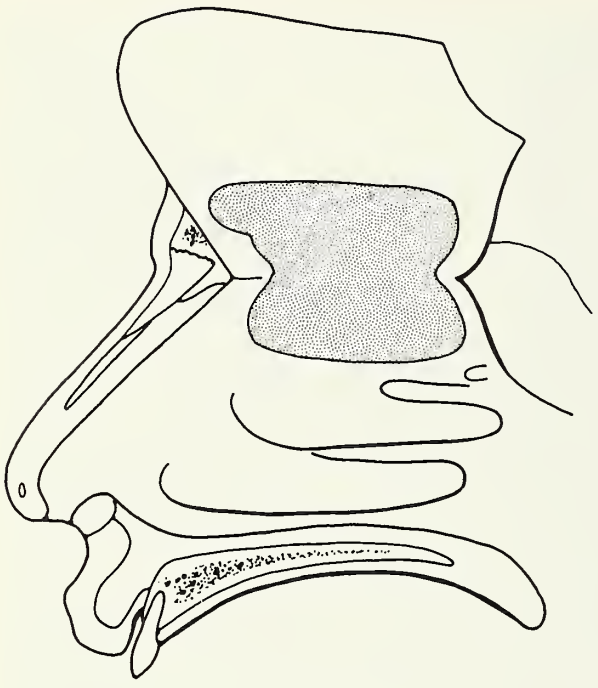


Figure 4
NASAL CAVITY
The shaded area is the usual distribution of olfactory mucosa in the upper nasal cavity. There is the rare ectopic migration of this specialized epithelium in the lower nasal turbinate area and the possible rare occurrence in the maxillary sinus.

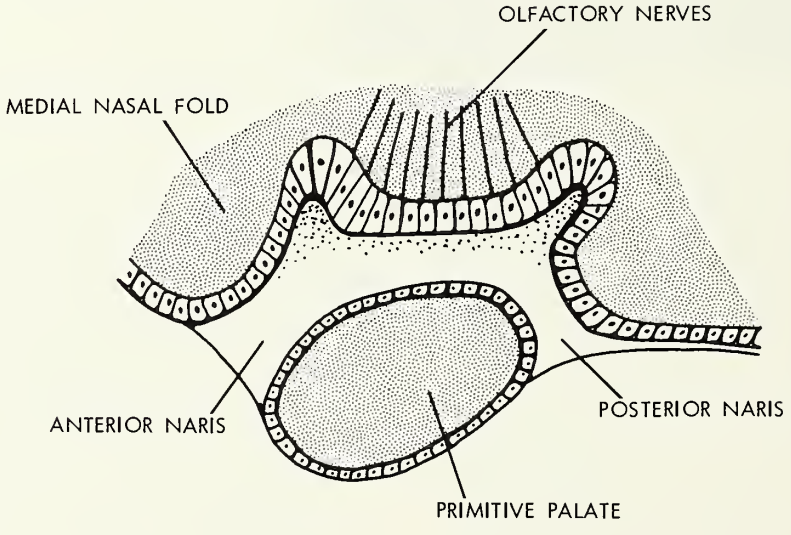


Figure 5
NASAL CAVITY
This shows the embryologic development of the bilateral nasal pits, in which the olfactory placode indents to begin formation of the nasal cavity and brings with it adjacent ectoderm to form the schneiderian mucosa.

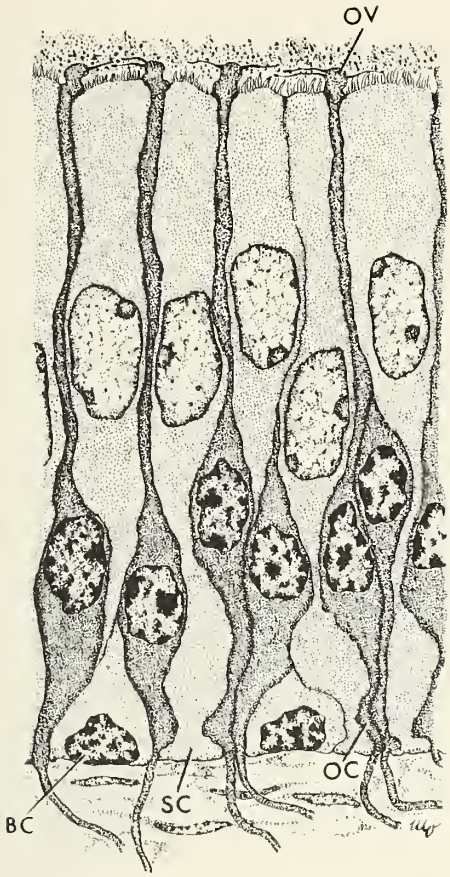


Figure 6
NASAL CAVITY
This schematic presentation delineates the bipolar neural cells with their mucosal ends consisting of the complicated olfactory vesicle and the proximal portion leading to unmyelinated nerves transversing through the cribriform plate to the olfactory bulb. Neuroectodermal-derived supporting cells and basal cells are depicted.

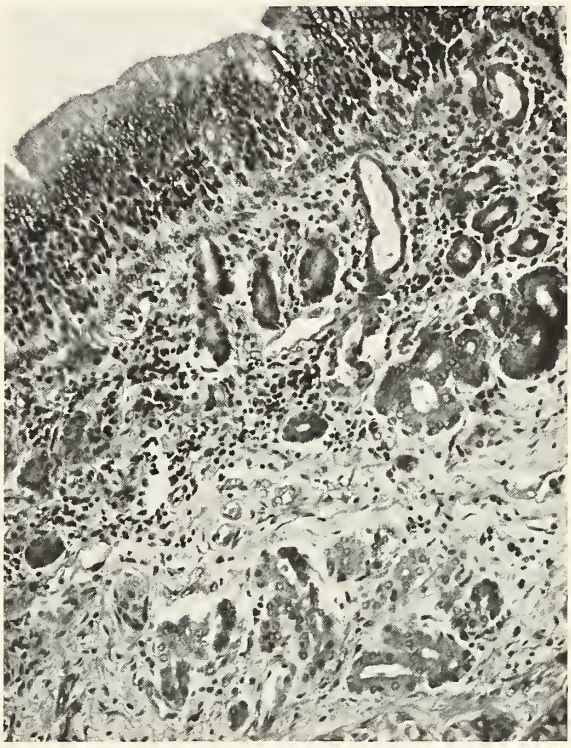


Figure 7
NASAL CAVITY
The addition of serous-like glands of Bowman in the lamina propria and subcutaneous tissue supports the previous presentation. The presence of these glands helps to identify the olfactory mucosa, since they lack the mucus elements of glands of the other areas of the nasal cavity. X160.

Pharynx

The pharynx includes the nasopharynx, oropharynx, and hypopharynx. The hypopharynx, which is not labeled in Plates I and II, is that portion of the pharynx which extends downward from the hyoid bone to the lower border of the cricoid cartilage or bone. At birth, the nasopharyngeal epithelium consists of a ciliated pseudostratifed columnar respiratory type. In later childhood, however, it undergoes a progressive squamous metaplasia (Ali) and this latter change, together with its prominent infiltration by lymphocytes, has been named lymphoepithelium (fig. 8). The mucosa throughout the remaining oropharynx and hypopharynx is a nonkeratinizing, stratified, squamous epithelium. The nasopharyngeal submucosa, particularly in early childhood, contains prominent, irregular corrugations of lymphoid tissue (adenoids) composed of lymph follicles and germinal centers. Beginning usually at puberty, the lymphoid tissue gradually diminishes quantitatively throughout life. Scattered

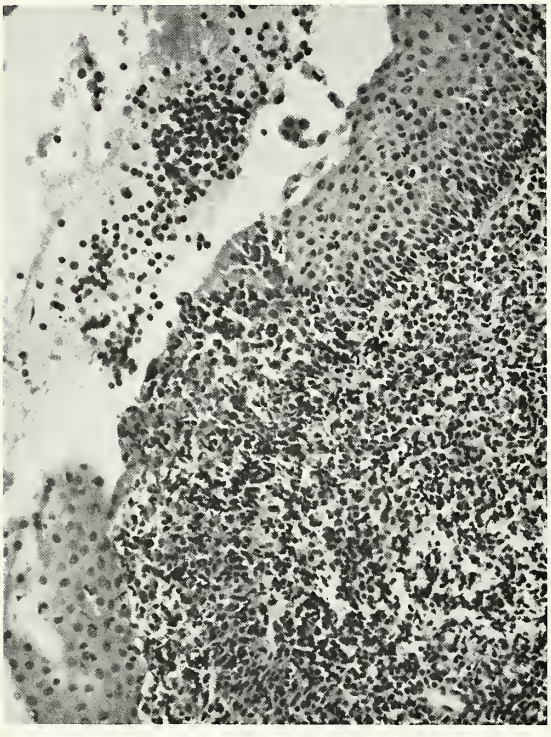


Figure 8
PHARYNX
This illustrates the tendency of lymphocytes to migrate through the mucosa, somewhat obliterating the demarcation between the two. These areas have been designated lymphoepithelium. This terminology and histology have been mistaken for a malignancy. X160.

mucoserous glands are found in the nasal pharyngeal submucosa, particularly concentrated in the area of the eustachian tube orifices. A rarely appreciated fact is the inclusion of anterior pituitary-like cells in the area of Rathke's pouch, a midline posterior superior vault indentation representing the embryologic remnant of the anterior pituitary migration (Melchionna and Moore). The oropharynx and hypopharynx may contain scattered aggregates of lymphoid tissue, but essentially the area is composed of scattered mucoserous glands interspersed in a submucosal, fibrovascular, areolar tissue with its deeper limits formed by the pharyngeal constrictor muscles.

Larynx

The epiglottis is unique for its central spoonlike, elastic cartilage perforated throughout by numerous foramina. The mucosa lining the lingual or anterior epiglottic surface is a nonkeratinizing, stratified, squamous epithelium in continuity with that of the posterior tongue (vallecula) and surrounding hypopharynx. The posterior or laryngeal epiglottic surface has a similar stratified squamous epithelium in its upper half, but gradually transforms into the ciliated pseudostratified columnar type characteristic of the internal laryngeal lining. The submucosa of the lingual epiglottic surface is a relatively loose areolar tissue, compared with the dense compact submucosal connective tissue of the laryngeal epiglottic surface. Mucoserous glands are abundant in the lower two-thirds of the epiglottis and occupy the foramina of the cartilage. The ventricular folds (false cords) are prominent, rounded folds and extend superolaterally into the aryepiglottic folds, forming an anatomic funnel from the epiglottic to the arytenoid cartilages. The ventricular fold mucosa is normally of ciliated respiratory type blending laterally with the stratified squamous surface of the aryepiglottic folds. The submucosa is rich in mucoserous glands embedded in a fibroareolar stroma admixed with strands of striated muscle fibers extending superiorly from the thyroarytenoid (vocalis) muscle. The ventricle and its upward saccular extension, both lined by ciliated respiratory mucosa, separate the true vocal cords (glottis) from the supraglottic structures. The true vocal cords are covered by a nonkeratinizing, stratified squamous epithelium which begins superiorly on the medial floor of the ventricle (superior arcuate line) and ends inferiorly at the lower edge of the thyroarytenoid muscle

(inferior arcuate line), blending into the ciliated mucosa that is continued onto the surface of the trachea. Immediately beneath the true vocal cord mucosa is the vocal ligament (Reinke's space), an essentially elastic tissue band devoid of mucoserous glands and containing only scant detectable vascular spaces. The anterior portion of the vocal ligament may contain symmetric nodules of elastic cartilage (Anson). The anterior portions of the vocal ligaments come together in the midline to form the anterior commissure. Directly anterior to this anterior commissure is the vertical thyroepiglottic ligament (Broyle's ligament), which represents the attachment of the epiglottis to the lower inner surface of the thyroid cartilage. This ligament reveals an aglandular zone of tendinous fibrous tissue that cushions the anterior commissure from the thyroid cartilage and forms somewhat of a barrier to the spread of superficial squamous cell carcinoma of the anterior commissure. Lateral to the vocal ligament is the prominent thyroarytenoid (vocalis) muscle. The thyroid, cricoid, and arytenoid cartilages are of hyaline type and are subject to ossification early in adult life. The epiglottis and the paired cuneiform and corniculate cartilages are elastic cartilages and normally do not undergo ossification.

EMBRYOLOGY

Nasal Cavity

The olfactory organ and the epithelium of the nose are of neuroectodermal and ectodermal origin, respectively. The olfactory organ arises at the embryo's fourth week of development as a thickening of ectoderm in the vicinity of the forebrain and bordering the stomodeum. The neuroectodermal thickening (olfactory placode) becomes a hollow invagination (olfactory pit) and this and the adjacent ectoderm become surrounded by

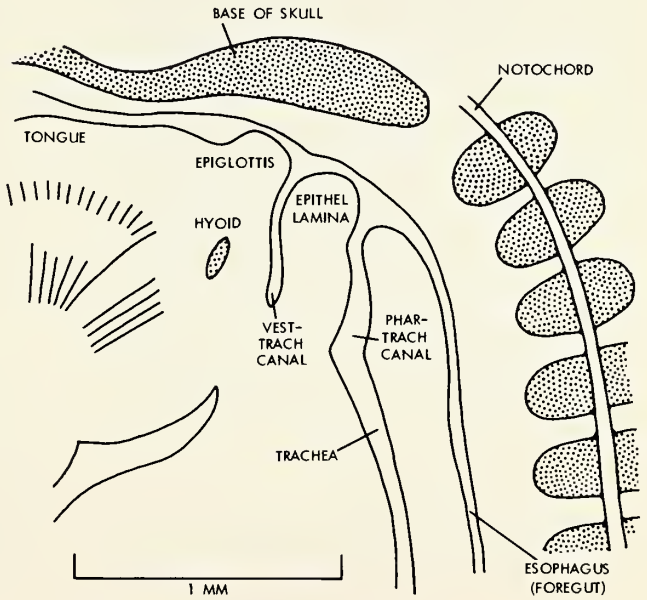


Figure 9
EMBRYOLOGY — PHARYNX AND LARYNX
This sagittal section in a seven weeks embryo demonstrates the pharyngeal-tracheal canal from which the trachea develops. Slightly later the superior vestibular tracheal pouch develops to form the larynx. These two canals merge to form the laryngotracheal complex. (Fig. 3 from Tucker, J.A. and O'Rahilly, R. Observations of the embryology of the human larynx. Ann. Otol. Rhinol. Laryngol. 81:520-523, 1972.)

mesodermal thickenings — the medial and lateral nasal processes on each side and the maxillary process below — thus forming the nasal cavity. Neuroectodermal cells in the upper part of this cavity send out processes to the forebrain which establish synaptic connections with the neuroblasts of the olfactory bulbs, the latter being hollow outgrowths of the floor of the cerebral vesicles which subsequently lose their cavity.

Paranasal Sinuses

The maxillary, ethmoid, and sphenoid paranasal sinuses are vestigial cavities at birth and develop further during the earlier years of life. The frontal sinuses are first noted in the neonatal period.

Pharynx and Larynx

The foregut is elongated with the development of the branchial arches in this vicinity (see section on Branchial Cleft Cysts) and becomes the pharynx and esophagus. A groove develops in the ventral wall of that part of the foregut which will become the lower part of the pharynx and the retrotracheal part of the esophagus. This groove then develops diverticula, which grow downward to form the trachea, bronchi, lungs, and larynx (fig. 9) (Tucker and O'Rahilly; O'Rahilly and Tucker).

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TUMORS SIMULATING NEOPLASIA OR OF QUESTIONABLE NEOPLASTIC CLASSIFICATION

NASAL AND PARANASAL POLYPOSIS

Swelling and polyposis of the sinonasal mucosa are produced in many different pathologic conditions in this anatomic area. They may be either benign or malignant and deserve histologic investigation.

Inflammatory polyps, single or multiple, may be due to allergy, but in the majority of cases the cause is obscure (Holopainen et al.). The etiology and pathophysiology is disputed (Dolowitz and Hecker), with the majority of investigators favoring some connective tissue dysfunction (due to an allergen), with retention of fluid within the stroma. The aglandular lamina propria, immediately beneath the mucosa, appears to be the initial area of involvement. In the pediatric age, sinonasal polyposis can be associated with cystic fibrosis of the pancreas (mucoviscidosis).

Grossly, the inflammatory polyp most often presents a soft, fleshy, lobular, gray to pink, translucent appearance, varying in diameter up to several centimeters. On rare occasions, because of their size and pressure, they may cause an erosion of adjacent sinonasal bony walls. The cut surface is usually gray, translucent, flat, moist, and mucoid, possibly with hemorrhage and cyst formation. The typical bulky inflammatory polyp apparently does not arise from the nasal septum, but most likely from the surface of sinus cavities, mainly the maxillary antrum. There is indecision as to whether the large inflammatory type polyps can arise from the lateral nasal wall and turbinate area (Blumstein; Dolowitz and Hecker). The choanal inflammatory polyp originates from the mucosa of the maxillary sinus and will extrude through the sinus ostia into the nasal cavity and then project through the posterior choana into the nasopharynx.

The histology of the acute inflammatory polyp will usually present a mucosal surface of essentially mucous goblet cells (fig. 10), rather than the normal predominant ciliated cell appearance of the respiratory membrane.

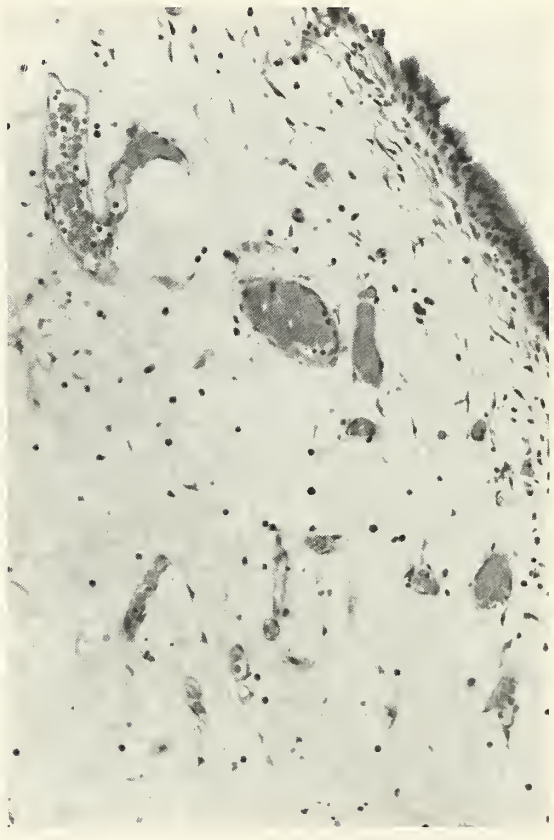

Figure 10
ACUTE INFLAMMATORY POLYP
This emphasizes the myxomatous stroma with scarce fibrocytes and mixed inflammatory cells. A vascular pattern is prominent. X160.

There may be a thickened eosinophilic basement membrane. The stroma has a myxomatous structure with a markedly edematous fibrillar composition and scattered fibrocytes. The vascular pattern will vary, but usually no mucoserous glands are present, attesting to the probable origin of the polyps from the lamina propria. The inflammatory infiltrate will vary from predominantly neutrophils to practically all eosinophils, or any mixture of inflammatory cells. Mast cells may also be prominent. The predominant inflammatory cell may suggest an etiologic agent, such as eosinophils for allergy or mast cells for vasomotor rhinitis, but this is not a foolproof diagnostic assumption. As the polyposis becomes more chronic, the mucosa may reveal squamous metaplasia that, on occasion, can cause differential problems with a papilloma (fig. 11) or a carcinoma. The stroma of a chronic inflammatory polyp may appear fibrous, which, together with scattered vascular structures, might make one consider histologically the diagnosis of juvenile angiofibroma. Rare cases will show amyloid type degeneration of the stroma in long-standing polyps. Also, in some chronic inflammatory sinonasal reaction and/or polyps, there is a glandular architecture suggesting an adenomatous neoplasm (fig. 12). This pattern

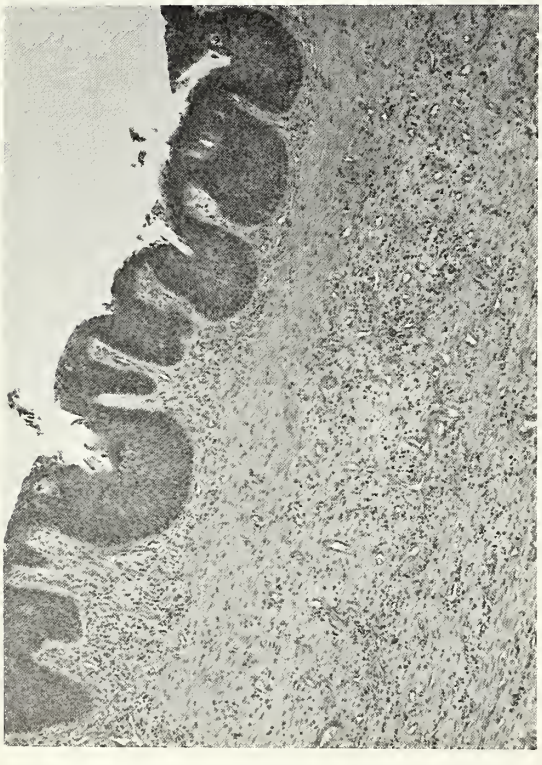

Figure 11
CHRONIC INFLAMMATORY POLYP
A chronic inflammatory polyp in the nasal cavity with squamous cell metaplasia of the mucosa, suggests an early so-called inverting papilloma. X63.

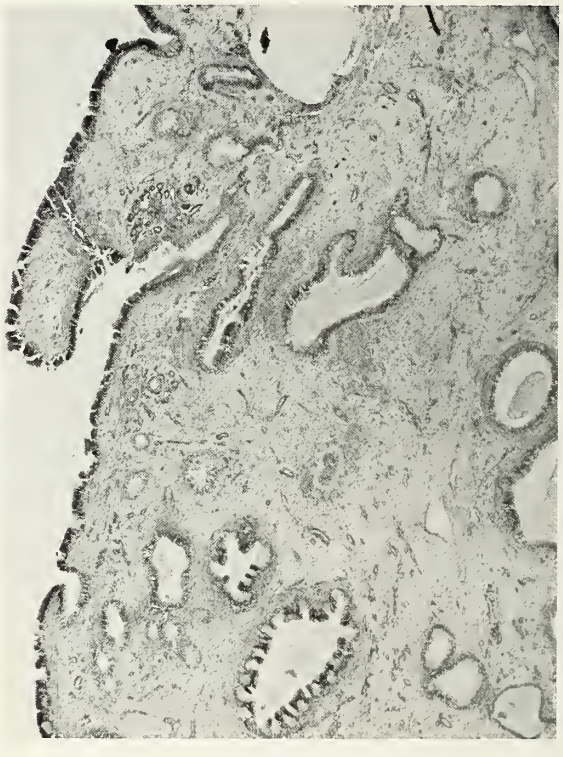

Figure 12
CHRONIC INFLAMMATORY POLYP
A chronic inflammatory polyp arising in the maxillary sinus presents an adenomatous pattern, due to cystic inclusions of surface mucosa in the stroma. The cilia noted on the surface of the cells lining these glandlike structures differentiates this lesion from an adenomatous neoplasm. X63.

is traced to a proliferation or indentation of surface mucosa into underlying stroma. Quite often, cilia can be identified on the glandlike cell surface, supporting the mucosal origin. Rarely, metaplastic cartilage or bone has been identified in otherwise ordinary inflammatory polyps.

Sinonasal Polyposis with Stroma Atypia

This particular inflammatory polypoid process is a clinically and grossly benign tumor, but histologically the unwary may diagnose it as a malignant neoplasm (Compagno and Hyams). It occurs mainly in young patients and involves those with a histology of chronic or allergic rhinosinositis. It is characterized by various sized foci of atypical stromal cells with a large hyperchromatic, sometimes multilobulated, nucleus. Nuclei may be multiple. The cytoplasm varies, but the atypical cells suggest a large myelofibroblast. Mitosis is absent. There are no cytoplasmic cross striations and the cellular glycogen content is minimal. The histologic structure along with the absence of local tissue destruction should distinguish this benign process from embryonal rhabdomyosarcoma, with which it is most often confused.

Inspissated Mucus

This condition is benign, but has a misleading histologic structure. It is a collection of impacted mucus and sinus cellular debris involving the cavity of any paranasal sinus. It occurs most often in the young adult or pediatric patient, usually with a history of chronic rhinosinositis from any cause. The inspissated mucus (which has been referred to as a "snotoma") may cause a radiologically demonstrated sinus opacity. Most often the maxillary or ethmoid sinuses are involved, but frontal and sphenoid sinuses may also be afflicted. If the patient is surgically explored, a firm, rubbery, gray to pink, translucent mass will be seen filling the sinus or nasal fossa. The mass will be easily removed from the cavity with rare evidence of bony destruction. The structure can be mistaken for a salivary gland mixed tumor or even rhabdomyosarcoma, because of the prominent background of homogeneous chondroid-appearing mucin positive material containing varying sized collections of acute and chronic inflammatory cells and desquamated respiratory mucosal cells. The rarity of local bone destruction both clinically and radiologically should help rule out a clinically aggressive neoplasm. Katzenstein and associates called attention to this entity and identified scattered hyphae consistent with Aspergillus in most of their cases. They felt that the fungus was probably the causative agent. However, it seems impossible to rule out the Aspergillus as an opportunist in this nutritional mucus collection.

Laryngeal Nodule and Polyp

These laryngeal tumors are well recognized as benign nonneoplastic processes and are essentially considered reactive to inflammation and/or trauma. Although perhaps more academic than practical, there may be a distinction made between the laryngeal nodule and the polyp.

The laryngeal nodule (screamer's node, singer's node) is a fusiform swelling, usually bilateral, involving the anterior or medial third of the true vocal cord, and usually follows chronic voice abuse in any age or sex. It has a benign, sometimes irregularly hyperplastic, squamous cell mucosa, beneath which is a fibrous avascular, aglandular, and nonedematous stroma (fig. 13). In many instances the laryngeal nodules disappear following vocal rehabilitation therapy.

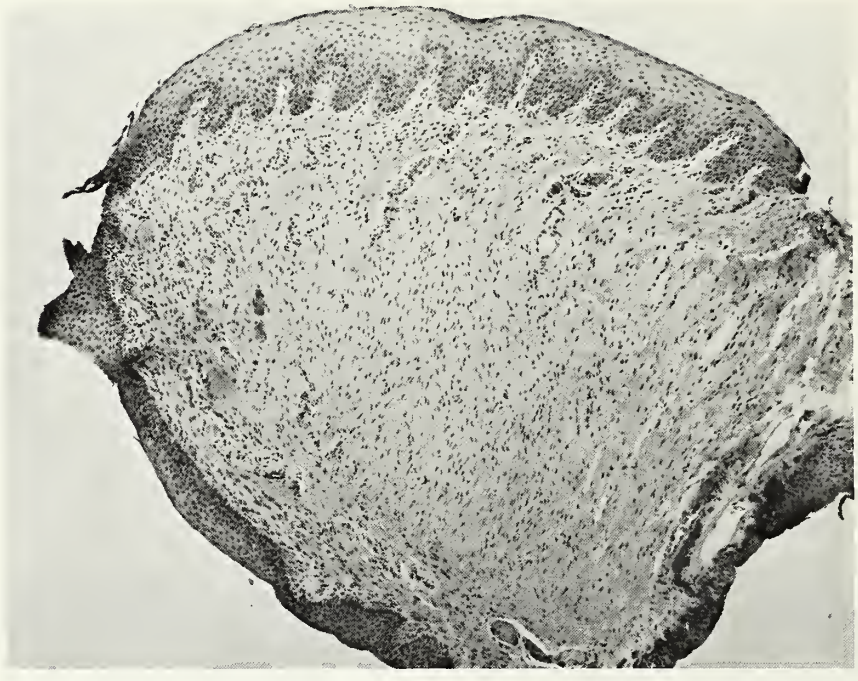

Figure 13
LARYNGEAL NODULE

The laryngeal nodule in this biopsy specimen is essentially a hyperplasia of the Reinke's space fibroelastic tissue. The overlying mucosa is usually a benign, slightly hyperplastic, squamous cell histology. X63.

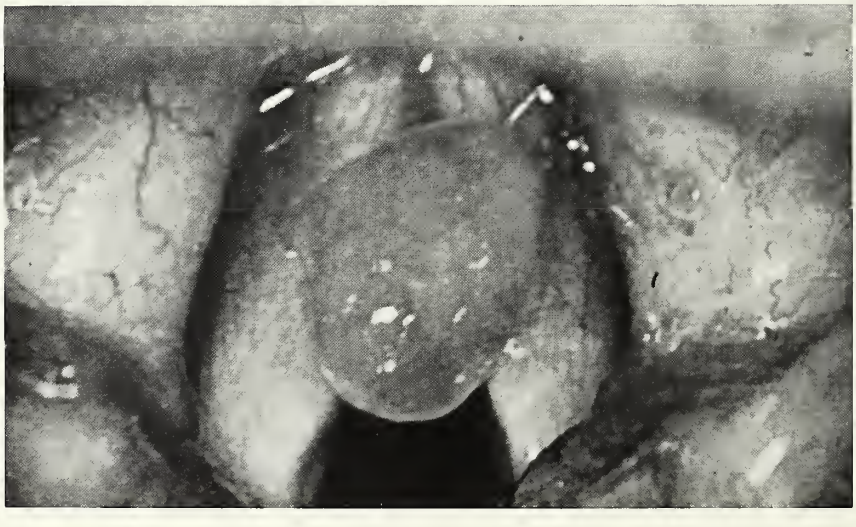

Figure 14
LARYNGEAL POLYP

Typical clinical appearance of a laryngeal polyp arising from the true vocal cord, which usually follows inflammation or chronic trauma, such as smoking or even possibly hypothyroidism. (Fig. 837 from Becker, W., Buckingham, R.A., Holinger, P.H., Korting, G.W., and Lederer, F.L. Atlas of Otorhinolaryngology and Bronchoesophagology. Philadelphia: W.B. Saunders Company, 1969.)

The laryngeal polyp is evident clinically by its endolaryngeal protruding tissue mass and its attachment to the larynx, possibly by a narrow pedicle (figs. 14, 15). Most frequently, it is a single lesion. The polyp usually arises from the true vocal cords, but it may originate in part or in whole from the adjacent ventricular fold or cavity (fig. 16). Laryngeal polyps may result from acute or chronic trauma, such as overzealous yelling and habitual smoking; infection, such as acute or chronic laryngitis; or endocrine dysfunction, such as hypothyroidism. In acute trauma, such as voice abuse, and occasionally with infection alone, evidence of recent hemorrhage may be seen grossly and histologically. The acute hemorrhagic polyp, however, is usually not seen clinically or histopathologically until several days or weeks following the initiating traumatic episode, and will reveal, microscopically, at this later time, a recanalization pattern and fibrin formation (fig. 17). The latter often is mistaken for amyloid when viewed on the standard hematoxylin-eosin histologic section. Differential histochemical staining for amyloid will prove the fibrin nature of the homogenous eosinophilic stromal material. Stromal hemosiderin pigment is not unusual. Those polyps that are the aftermath of chronic trauma (habitual smoking, chronic infection) and hypothyroid disorders will consist histologically of a myxomatous morphology usually devoid of inflammatory cells or

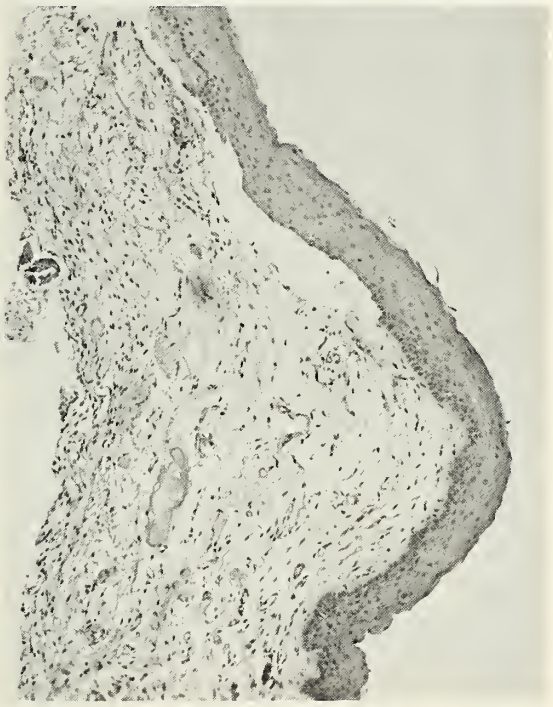

Figure 15
(Figures 15 and 16 are from the same patient)
INFLAMMATORY LARYNGEAL POLYP
This inflammatory laryngeal polyp is similar to the one shown in figure 14. X63.

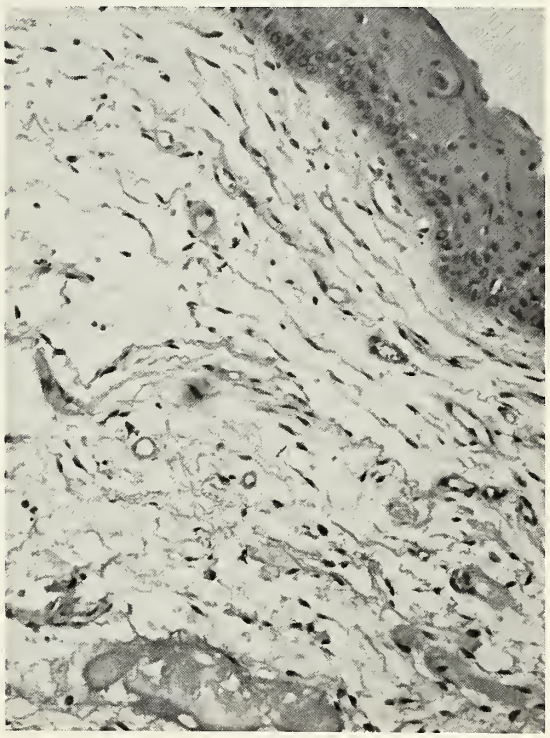

Figure 16
INFLAMMATORY LARYNGEAL POLYP
Occasionally, this type of laryngeal inflammatory polyp will arise from the edge of the ventricular fold or the floor of the ventricle. X160.

hemorrhage (fig. 15). Occasionally, micromorphology will suggest a neoplastic myxoma process (fig. 18), but the experience of the AFIP Otolaryngic Tumor Registry (OTR) confirms that this histology supports a reactive lesion. Recurrence is possible, particularly in the untreated cases of hypothyroidism. The occasional notation of benign cartilage in the stroma of the laryngeal nodule or polyps probably represents the inclusion of normal elastic cartilage normally present in the anterior portion of the true vocal cord (Anson) or in the posterior area portion of the local arytenoid cartilage vocal process. The overlying mucosa of the nodule and polyp can reveal a cytologically benign hyperplasia and, rarely, a dysplastic or malignant histology. The therapy (Strong and Vaughn) may be nonsurgical, particularly with the nodule, but the polyps will most often require removal to facilitate a return to normal phonation. Ash and Schwartz have proposed a chronologic progression from the laryngeal nodule to the polyp and although this is a clinical possibility, the AFIP-OTR experience supports two separate pathogenesis.

An occasional nonneoplastic nodule in the true vocal cord or its vicinity may represent a manifestation of rheumatoid arthritis (Friedman and Rice) or gout (Marion et al.).

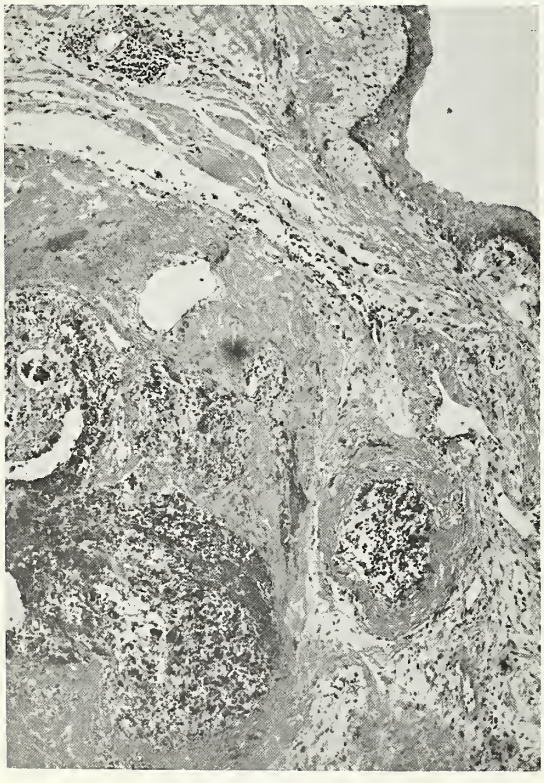

Figure 17
TRUE VOCAL CORD POLYP
Ten days after vocal cord trauma (overzealous yelling), hemorrhage had resolved with recanalization and fibrin formation. The latter material often is mistaken for amyloid, but will be negative with the Congo Red stain. X63.

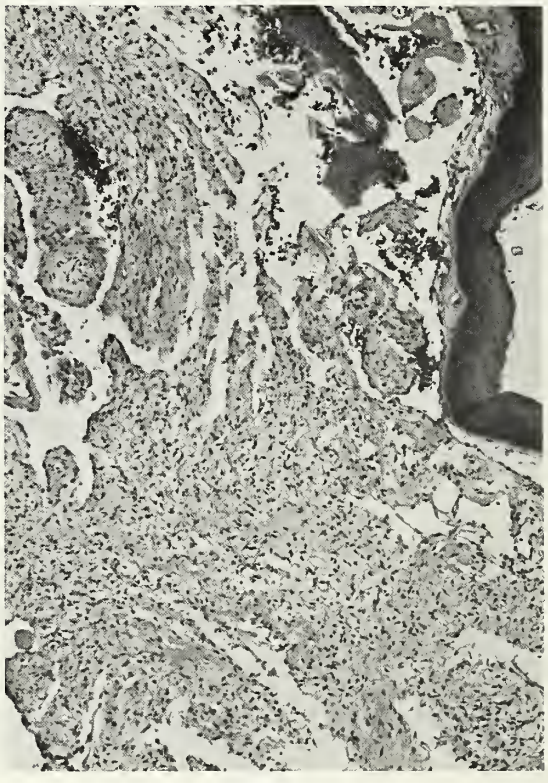

Figure 18
CHRONIC TRUE VOCAL CORD POLYP
Although this chronic true vocal cord polyp suggests a myxomatous neoplasm, it apparently represents a chronic inflammatory process and, while it may recur locally, there has been little evidence of aggressive behavior. X63.

"Contact" Ulcer

The "contact" ulcer must be mentioned as a tumor-like condition of the larynx occurring most often on the posterior true vocal cord in the area of the vocal process of the arytenoid cartilage, frequently bilateral, and resulting from voice abuse. The chronic "throat clearer" is a good candidate, but occasionally it results from chronic regurgitation of gastric contents such as in achalasia (Ward et al.). Microscopically, there is surface mucosal ulceration with achronic vascular granulation tissue base and surrounding surface reactive pseudoepitheliomatous hyperplasia which may be mistaken for well differentiated squamous cell carcinoma (fig. 19). The clinical chronicity and the infrequent origin of squamous cell carcinoma from the posterior true vocal cord should help in the differential diagnosis. Vocal rehabilitation rather than surgical removal is the recommended treatment. The "intubation" granuloma of the posterior true vocal cords presents a more acute granulation tissue reaction and the history of recent mechanical trauma such as upper airway intubation is diagnostic.

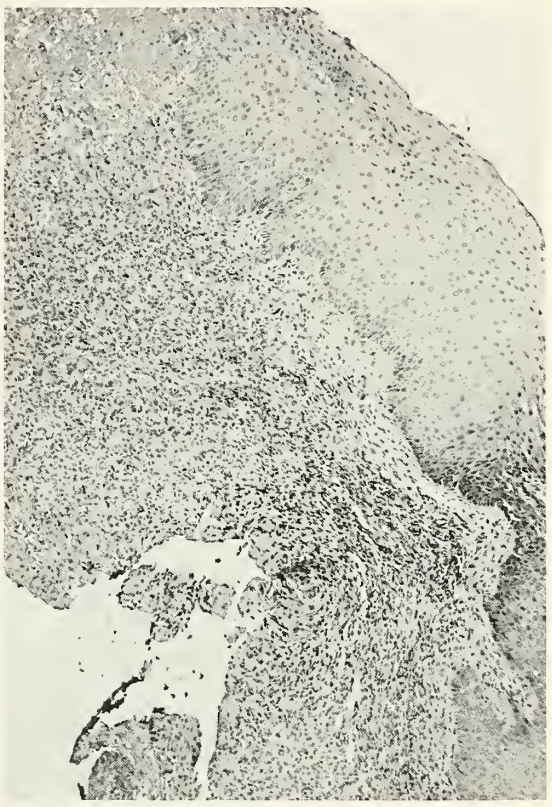

Figure 19
"CONTACT" ULCER
A "contact" ulcer, which usually involves bilaterally the posterior third of the true cord, reveals surface mucosal ulceration, a base of chronic vascular granulation tissue, and adjacent pseudoepitheliomatous hyperplasia. Occasionally, this histology is mistaken for a malignancy. X63.

CYSTS

A cyst can be part of a neoplastic or nonneoplastic pathologic process and it is difficult to classify even the nonneoplastic variety. The true neoplastic cystic lesions of interest in the upper respiratory tract will be discussed later in their appropriate anatomic area. In this section, the nonneoplastic cysts, such as the epidermal inclusion cysts, Rathke's pouch lesions, midline pharyngeal cysts, mucoceles, and branchial cleft cysts will be discussed as they relate to the tumor simulating neoplasia in the upper respiratory tract. Nonodontogenic cysts of the nasopalatine and globulomaxillary area are presented in Fascicle 24, Second Series, Intraosseous and Parosteal Tumors of the Jaws. Thyroglossal duct cysts are defined in Fascicle 4, Second Series, Tumors of the Thyroid Gland.

Epidermal Inclusion Cyst

This benign nonneoplastic cystic entity is seen essentially anywhere in the upper respiratory tract. They are erroneously referred to as dermoid or sebaceous cysts.

The dermoid is considered later in the section on Teratoid Neoplasia. The sebaceous cyst (fig. 20) is a skin adnexal cyst (synonym: pilar cyst) (Lever and Schaumburg-Lever), occurring primarily in the scalp area and uncommon in frequency when compared with the epidermal inclusion cyst. Epidermal inclusion cysts are most likely due to inclusions of squamous epithelium in the process of embryogenesis, although traumatic inclusions and inflammation are possible causes. Cholesteatoma of the temporal bone, particularly the middle ear, is an example of the latter. Epidermal inclusion cyst occurrence in the palatine, lingual, and paralingual tonsillar tissue suggests an origin by inclusion of a squamous cell-lined surface crypt.

Clinically and grossly, a well demarcated cyst is apparent with a content of creamy, pale material, representing the desquamated keratin debris of the lining mucosa. The micromorphology is that of a benign, usually thin, keratinizing, stratified squamous cell epithelium (fig. 21). The cyst is surrounded by a fibroareolar tissue containing no adnexal structures.

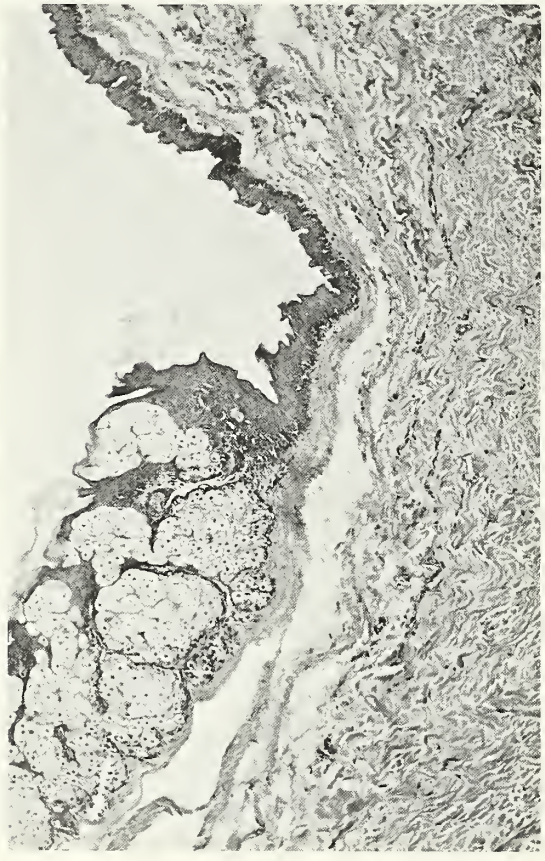

Figure 20
SEBACEOUS CYST
This rare true sebaceous cyst contains sebaceous glands in the wall and a benign squamous cell proliferation. X63.

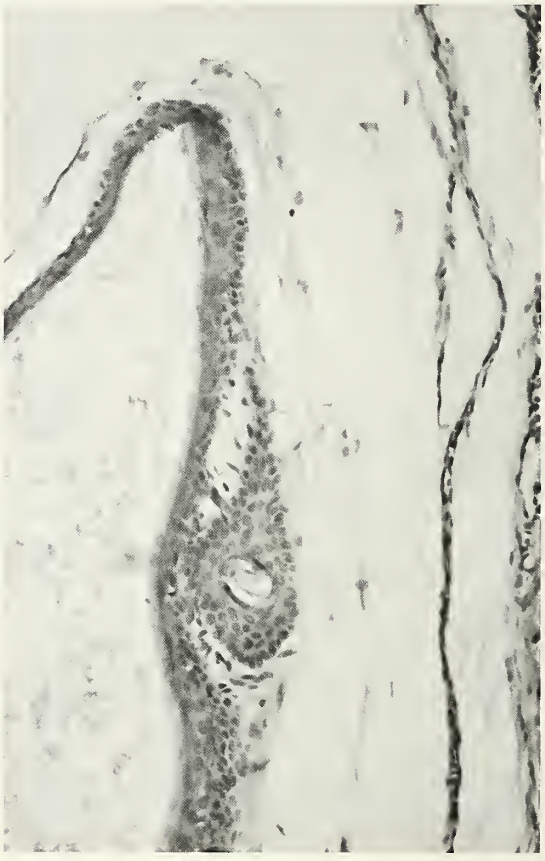

Figure 21
EPIDERMAL INCLUSION CYST
A portion of an epidermal inclusion cyst consisting of a keratinizing thin, stratified squamous epithelial lining and keratin debris within the lumen. X160.

Embryologic Remnants in the Nasopharyngeal Region

Persistence of Rathke's pouch as a cyst and the development of tumor-like formations (craniopharyngiomas) are discussed in Fascicle 2, Second Series, Tumors of the Central Nervous System.

Probably representing a residuum of Rathke's pouch, a pharyngeal pituitary was found at autopsy by Melchionna and Moore in 51 of 54 cases in which they removed a block from the region of the vomerosphenoidal articulation for histologic examination. In most cases, it was located in the midline deep in the mucosa or in the periosteum and was from 0.22 to 6.62 mm in length and 0.21 to 1.15 mm in width. A majority of the pharyngeal pituitaries revealed small numbers of pituitary eosinophilic or basophilic cells, but in most cases the epithelial cells were undifferentiated. It is felt unlikely that the pharyngeal pituitary contributes to any significant function or pathologic change (figs. 22-24).

Midline Pharyngeal Cyst

The embryonal pharyngeal bursa is an invagination of ectoderm that takes place in relation to the tip of the primitive notochord and is found in about 50 percent of fetuses over 15 mm in length. It is situated posterior to the region of Rathke's pouch at about the junction of the vault with the posterior pharyngeal wall and extends between the heads of the longus capitis muscles, just above the upper edge of the superior constrictor muscle.

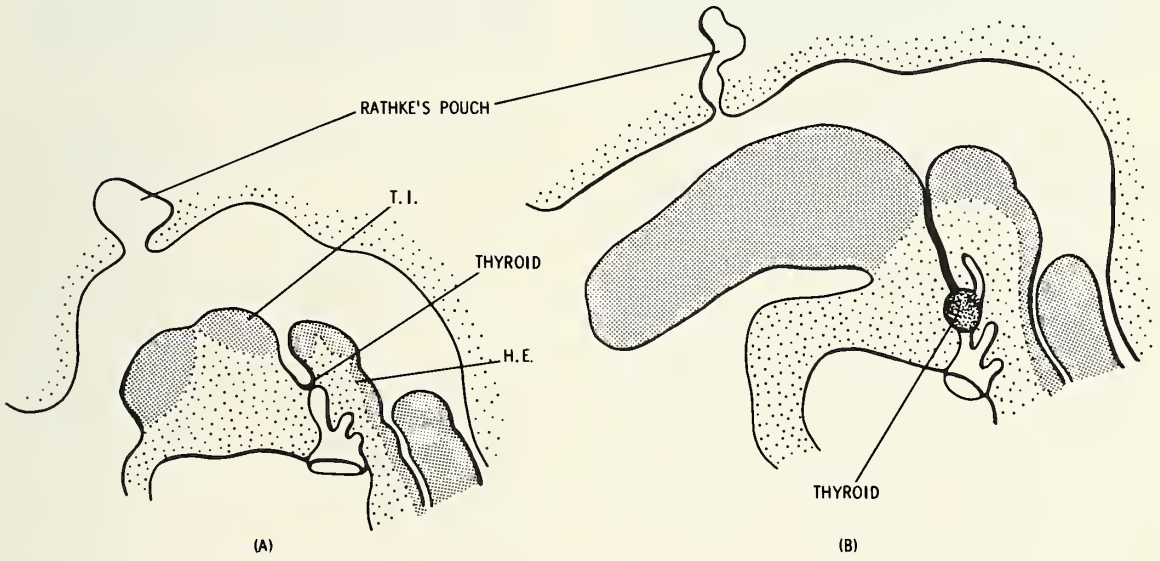

Figure 22
MIDLINE PHARYNGEAL CYST

A schematic section of the embryonic pharynx emphasizes the development of Rathke's pouch. The persistence of this pouch may lead to a cystic tumor of the nasopharynx. This is the point of origin of the craniopharyngioma as well as the ectopic anterior pituitary cells that, rarely, may be the origin of a nasopharyngeal and/or sphenoid sinus neoplasm. (Fig. 17 from Davies, J. Embryology of the Head and Neck in Relation to the Practice of Otolaryngology. Washington, DC: American Academy of Otolaryngology, 1957.)

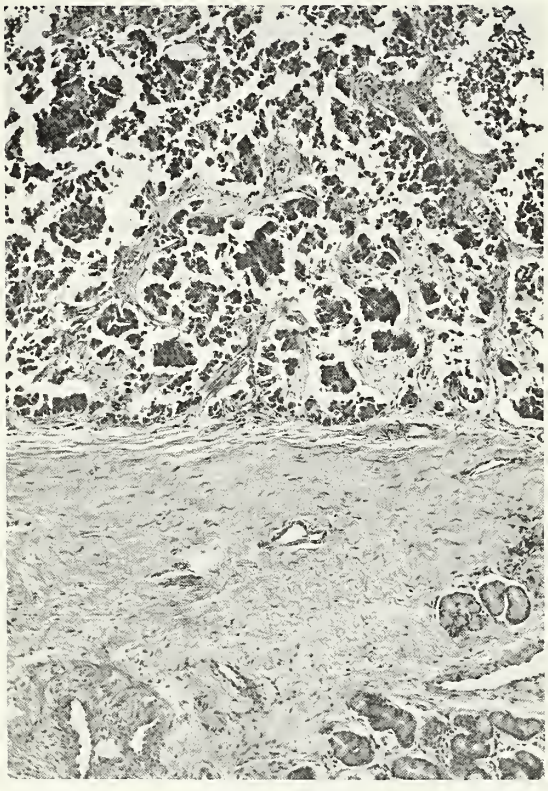

Figure 23
(Figures 23 and 24 are from the same patient)
CHROMOPHOBE ADENOMA
This is a chromophobe adenoma of pituitary gland type arising from the floor of the sphenoid sinus and nasopharyngeal roof. X60.

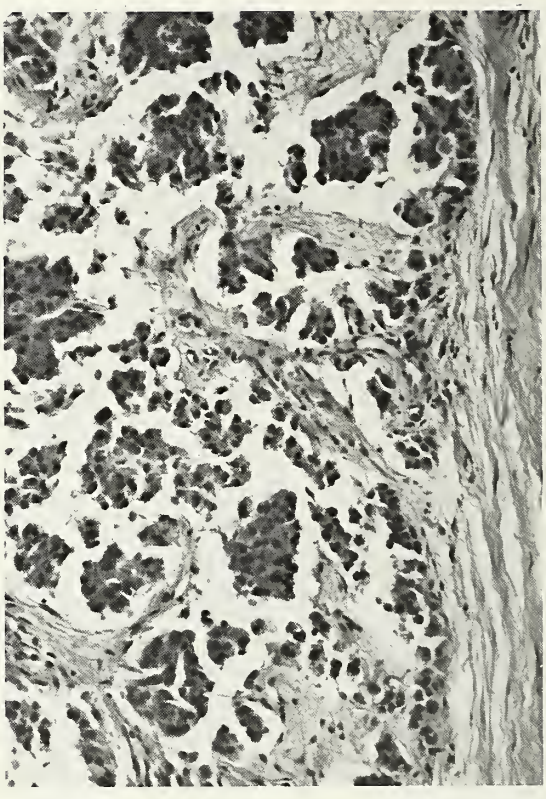

Figure 24
CHROMOPHOBE ADENOMA
A higher power magnification of figure 23. X160.

Cysts derived from the embryonal pharyngeal bursa may be found in any age group. They are separated from the nasopharyngeal mucosa by a membrane or by the fibers of the longus capitis muscle and hence will not be removed at adenoidectomy. The median pharyngeal recess is a shallow depression formed as the analogue of the pharyngeal tonsil. Cysts derived from this structure are included in the adenoid and removed with it (Guggenheim). The term "Tornwaldt's bursa" has been applied to either of these embryologically-derived cysts, the embryonal pharyngeal bursa, or the median pharyngeal recess in the pituitary region (fig. 25).

Branchial Cleft Cyst (Lateral Cervical Cyst)

Four ridges appear in the pharynx of the 5 mm fetus. These are the branchial arches. Between them and extending inferiorly are formed the four branchial clefts or grooves (ectodermal or outer side) and the branchial pouches (endodermal or inner side). Cysts of sinuses apparently result from the persistence or reduplication of ectodermal and/or endodermal branchial structures. Among the theories of origin of the branchial cleft cysts and sinuses is the so-called inclusion theory of Bhasker and Bernier, championed

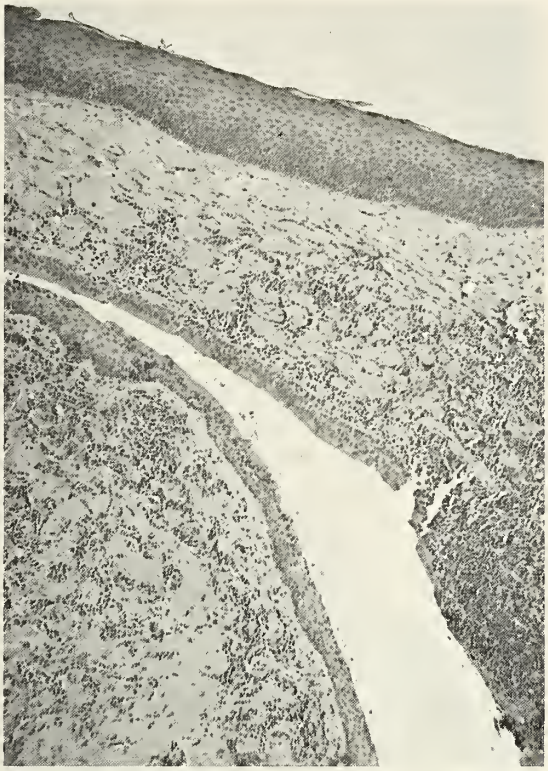

Figure 25
CYSTIC LESION OF THE NASOPHARYNX
In this cystic lesion of the nasopharynx, considered a Tornwaldt's bursa, there is a lining of respiratory columnar and benign squamous cells. X63.

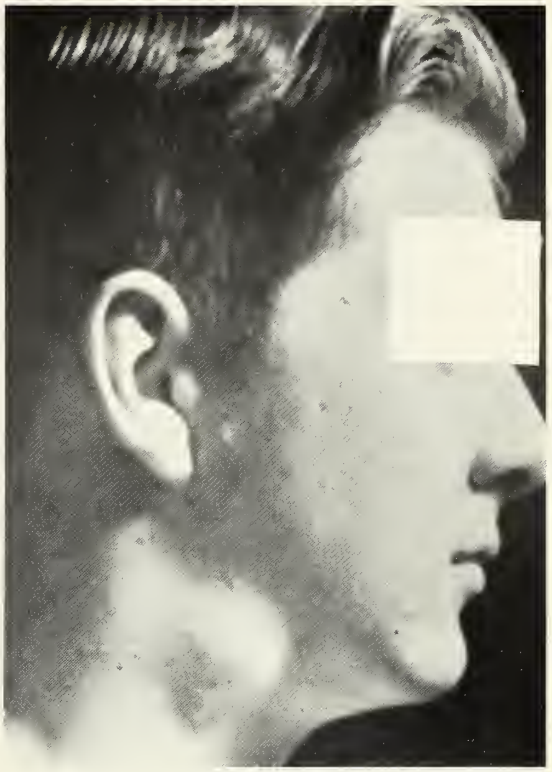

Figure 26
BRANCHIAL CLEFT CYST
A young man presented with a painless midneck mass, present for two years, that had recently enlarged. The position at the midanterior border of the sternocleidomastoid muscle is a typical location of the branchial cleft cyst.

also by Maran and Buchanan, that the entity arises from entrapped ectopic epithelium in cervical lymph nodes. Literally tens of thousands of lymph nodes of the neck area have been examined in the AFIP-OTR material and none has shown evidence of benign epithelial squamous cell inclusions. All the cervical lymph nodes with suggested squamous cell inclusions supported histologically a diagnosis of metastatic squamous cell carcinoma. The combined branchial apparatus and cervical sinus theory (Davies) seems more embryologically feasible and acceptable to explain the genesis of the branchial cleft cysts.

The first branchial cleft or groove normally gives rise to the external auditory meatus. Cysts, sinuses, and fistula forming from maldevelopment of the first branchial cleft will be discussed later, together with tumors of the external ear. Persistence or duplication of the second branchial cleft presumably accounts for the superficial position of most branchial cleft cysts or sinuses at the level of the hyoid and deep to the sternomastoid (fig. 26). Occasionally a branchial cleft cyst may be found near the pharynx in relation to one or other palatine tonsil, or even laterally in the nasopharynx. In these latter cases, an origin from the branchial pouch, the en-

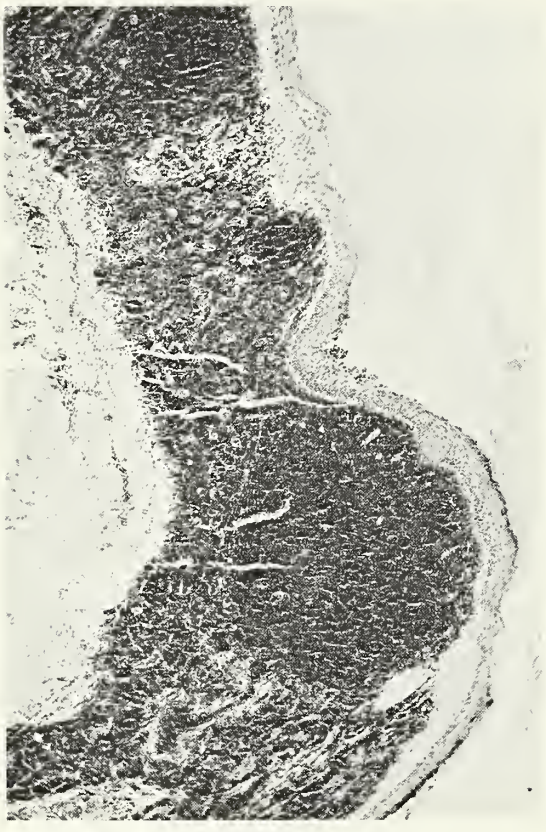

Figure 27
BRANCHIAL CLEFT CYST
This is the typical histopathology of the branchial cleft cyst with a lining of thin, keratinizing, squamous cell epithelium and an underlying lymphoid infiltrate which does not have the anatomy of a normal lymph node. X63.

dodermal depression between the branchial arches, may be assumed. In the cases where the branchial cleft cyst is superficial in the neck, there may be a connection with the pharynx by a fibrous pedicle (Willis).

Branchial cleft cysts are unilocular, with yellow mucoid contents composed of desquamated keratin squame. There may be an attached sinus tract either opening on the skin surface or following a tract to the supraglottic or tonsillar fossa area. The lining epithelium is usually of histologically benign, keratinizing, stratified squamous type. External to the epithelium is a zone of lymphoid tissue usually composed of lymphoid follicles with germinal centers. There are no peripheral lymphatic sinusoids similar to those seen in the pericapsular areas of lymph nodes. The proximity of keratinizing squamous epithelium to lymphoid tissue is reminiscent of the crypts of the palatine tonsil and other parts of Waldeyer's pharyngeal ring (fig. 27).

The appearance of a cystic squamous carcinoma in the neck sometimes gives rise to the suggestion that the neoplasm has arisen by malignant degeneration of a branchial cleft cyst. A study by Compagno and associates of 22 cases of cystic squamous cell carcinoma of the neck, suspected of being primary malignant branchial cleft cysts, demonstrated that 19 subsequently manifested another primary source of the neoplasm, usually in the Waldeyer's ring area. The tonsil quite often reveals the occult primary (Micheau et al.). There is as yet no indisputable evidence for the occurrence of a malignant form of branchial cleft cyst.

Laryngeal Cyst

There are essentially three types of cysts encountered in the larynx, usually located supraglottically, each of which can be correlated with occurrence in a certain age group. The first type is considered a congenital cyst, is seen in the newborn, and may cause emergency airway problems at birth. The pathology reveals a cyst or cysts of varying size, which are filled with clear fluid and lined by a ciliated pseudocolumnar epithelium. The pathogenesis supports a cystic growth from embryologically misplaced laryngeal epithelium.

The second type of laryngeal cyst occurs more often in the teenage or young adult age group, is usually found in the aryepiglottic fold, is lined by benign, keratinizing, squamous cell epithelium, and contains milky or cloudy fluid or keratin debris. This laryngeal cyst is considered possibly a remnant of the upper end of a branchial cleft sinus derived from the third or fourth branchial cleft.

The third type of laryngeal cyst usually occurs in patients over 60 years of age. The lesion is lined by histologically benign oncocytic cells and is considered to be derived from a cystic distention of an oncocytic metaplasia of the supraglottic mucoserous glands. The tumor may be considered by some as an oncocytoma or oxyphil adenoma.

Treatment for cysts of the larynx is simple surgical removal, mainly to relieve airway obstruction, which may be an emergency situation. Recurrence, particularly in the older adult group, may necessitate repeat removal. In the AFIP-OTR material, no case of malignant change has occurred.

MUCOCELE

A sinonasal area mucocele (to be distinguished from the oral cavity mucocele due to an obstructed minor salivary gland) results from an increase of pressure within a paranasal sinus cavity secondary to a blocking of the ostium from inflammation or trauma. The increased intracavitary pressure may not cause disruption of the bony paranasal confines, but, particularly in the maxillary antrum, there may be a herniation of the mucosa into the submucosal tissue adjacent to the bony wall forming a so-called internal mucocele that presents as a radiologic cystic structure in the floor of the antrum. The more dramatic presentation is the external mucocele propulsion through a defect in the bony walls of the paranasal sinus into a subcutaneous or intracranial area. This may be due to a congenital anomaly, previous sinus infection, sinonasal surgical manipulation, trauma, long-standing allergy, or osteomas involving the sinonasal area. Proptosis is not unusual with external mucoceles, particularly when they involve the maxillary antrum, frontal, or ethmoid paranasal sinus. The pyocele of the paranasal sinus results from infection of a mucocele.

Histopathologically, the epithelium of the sinus or the mucocele may be somewhat flattened from the normal pseudostratified columnar ciliated respiratory appearance. Of particular interest is the histologic picture of a mucocele, usually of the frontal sinus, that extends into the frontal lobe of the anterior cerebral fossa (fig. 28). The cystic mass will involve the cerebrum and is lined by respiratory type mucosa, but without any surrounding inflammatory reaction in the brain tissue. The histologic identification of a limiting leptomeninges surrounding the mucocele sac is difficult to define. If hemorrhage occurs within the cavity of the mucocele, the likelihood of a concurrent cholesterol granuloma must be considered.

LARYNGOCELE

Laryngoceles are nonneoplastic tumors originating from a normal pouch (the saccule or appendix) that arise on each side of the ventricle between the false and true vocal cords. They may present as a lateral neck mass (external laryngocele) when they project upward between the false cord and the thyroid cartilage and laterally through the hyothyroid ligament. When, instead of pushing laterally, they extend medially through the aryepiglottic and ventricular folds into the laryngeal lumen, they are considered inter-

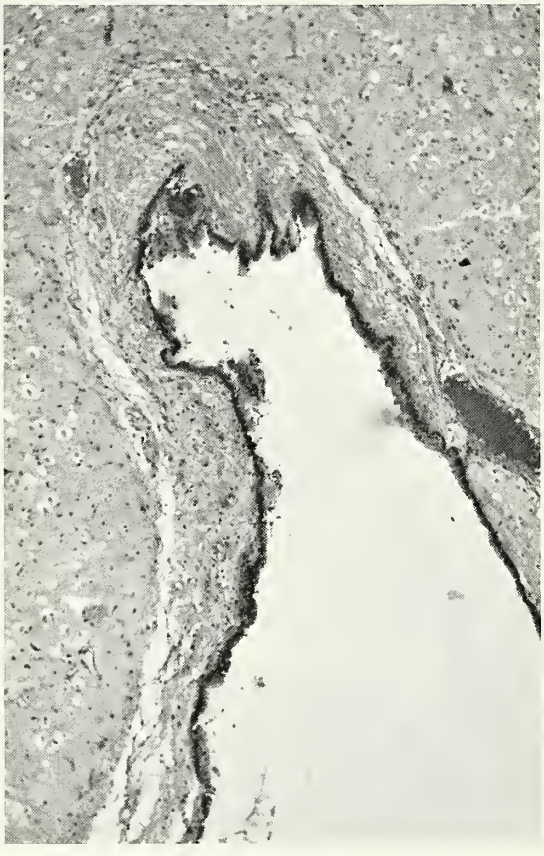

Figure 28
MUCOCELE
Note the absence of a reaction in the surrounding cerebral tissue and no definite leptomeningeal layer in this frontal sinus external mucocele that has invaginated into the frontal lobe. X63.

nal laryngoceles. Stell and Maran, in an excellent review of laryngoceles, found them in patients of all ages, but concentrated in the fifth and sixth decades, decidedly male-oriented, and with no racial preference. Most cases were unilateral, with a 15 percent incidence of bilateral involvement. Occupations such as horn and glass blowing did not seem significant, but neoplasia (carcinoma and papilloma) were apparently frequent as a causative relationship. The laryngopyocele represents the laryngocele filled with pus. The histologic structure of the laryngocele is that of the extended propulsion of the normal saccule which consists of a mucosa (ciliated pseudostratified columnar epithelium) and underlying loose fibroareolar tissue, perhaps containing clusters of mucoserous glands. Occasionally, the designation of "prolapse of the ventricle" is utilized for a mucosa-lined cystic mass in the supraglottic area occurring usually in older adults. These cystic adult supraglottic tumors will be discussed in the section on Adenomatous Tumors of the Larynx.

INFECTIVE GRANULOMAS

Rhinoscleroma

Rhinoscleroma is a chronic granulomatous disease usually beginning in the upper respiratory tract, with a characteristic histologic appearance in which Klebsiella bacilli are present within histiocytic cells. It is essentially a disease of the poor, unhealthy living conditions and malnutrition apparently foster a suitable environment for the initiation and spread of the disease.

Incidence. The disease is endemic in well defined geographic areas. It is most commonly found in Egypt, South and Central America, and North and Central Africa, but it also occurs in the United States, where statistics on incidence are unavailable. Incidence of cases in eastern European countries has decreased in recent years (Kerdel-Vegas et al.). Sex involvement is equal. Highest incidence is in the 15 to 35 years age group.

Etiology. Gram-negative organisms of Klebsiella rhinoscleromatosis are found in the lesion by microscopy and culture. Serologic reactions to such organisms are obtained in affected patients by complement fixation tests and may be utilized in assessing the therapeutic response in the patient.

Site. Rhinoscleroma initially appears on the nasal septum, often fills the nasal cavity (fig. 29), spreads posteriorly to the nasopharynx, and may involve the ethmoid paranasal sinuses, orbit, larynx, trachea, bronchi, or even the middle ear (Barbary et al.). Extension to the skin of the nose, upper lip, and cervical lymph nodes may occur.

Gross. The clinical appearance is that of nodules of thickened mucosa suggesting a surface crusting exudate; however, frank ulceration of the masses is rare. The masses are pale, with a cartilaginous firmness. A progression of the gross changes of the disease from a rhinitic stage, through an infiltrative stage, to a nodular stage is described (Reyes; Stiernberg and Clark; Shum et al.).

Microscopic. The surface of the cartilaginous-like mass will be a prominent pseudoepitheliomatous hyperplastic mucosa (fig. 30). The submucosa is thickened by a granulomatous infiltration in which plasma cells and lymphocytes are prominent, possibly with large numbers of Russell bodies. Characteristic of the lesion is the Mikulicz cell, the number of which may vary from occasional to large groups occupying most of the submucosa (fig. 31). These are large polygonal cells with clear or faintly vacuolated to foamy cytoplasm. The cytoplasm of these cells frequently contains Gram-negative bacilli (Klebsiella), often emphasized in Gram or Warthin-Starry stained paraffin sections (fig. 32). In many cases, however, such organisms cannot be readily demonstrated. Positive results can be most reliably attained by tissue fixation and then embedding in Araldite as for electron microscopy preparation, cutting sections at 1-2 microns and staining with toluidine blue. Gumprecht and associates demonstrated an immunoperoxidase technic for the identification of

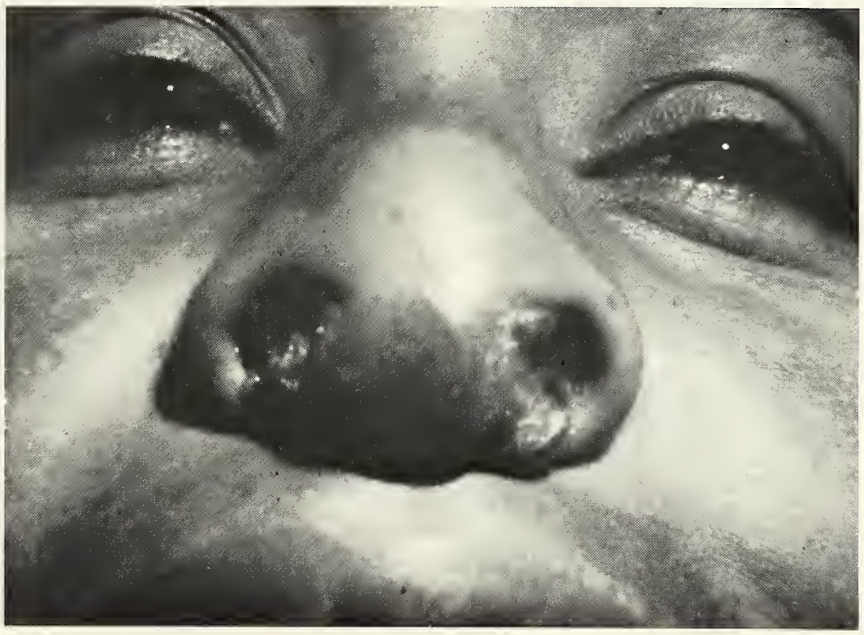

Figure 29
RHINOSCLEROMA
The presentation of rhinoscleroma of the nasal cavity with the prominence of the lower external nose (von Hebra nose), caused by granulation tissue in the anterior lower nasal cavity.

Figure 30
(Figures 30-32 are from the same patient)
RHINOSCLEROMA
This firm mass is from the nasal cavity of a Latin American adult. The surface is composed of pseudoepitheliomatous squamous cell hyperplasia. X63.

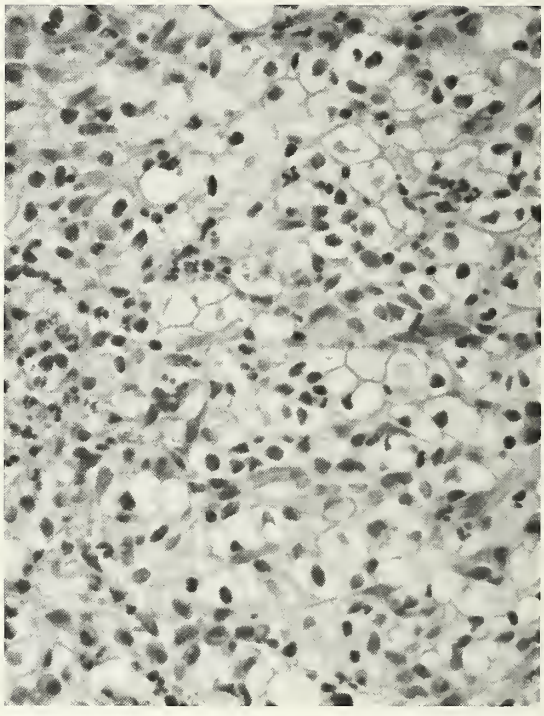

Figure 31
RHINOSCLEROMA
Higher magnification of the previous illustration depicts the Mikulicz cell as a large histiocyte with a faint, sometimes "moth-eaten," cytoplasm. X400.

rhinoscleroma. Dense bands of collagenous connective tissue eventually spread throughout the lesion, giving rise to the cartilaginous consistency.

Prognosis. If untreated, the disease may progress to produce grotesque lesions. Death may occur, particularly by obstruction of the airway. Treatment with tetracycline or broad spectrum antibiotic may be effective in arresting the progress of the condition. Surgery for the acute disease processes may prove disastrous, with dissemination of the disease (Kerdel-Vegas et al.). Two cases of squamous carcinoma developing at the site of established rhinoscleromatous lesions have been described (Attia).

Rhinosporidiosis

Rhinosporidiosis is a chronic disease of the upper respiratory tract, conjunctivae, tracheobronchial tree, genital area, and esophagus. It is characterized by the formation of persistent polyps and is caused by a fungus, Rhinosporidium seeberi. This fungus has not been cultured on artificial media, nor has it produced infection when inoculated in laboratory animals.

Spread. The disease is endemic in India and Sri Lanka and occurs only sporadically in other parts of the world. There have been 36 primary infections recorded in the United States. All ages are affected, but it occurs

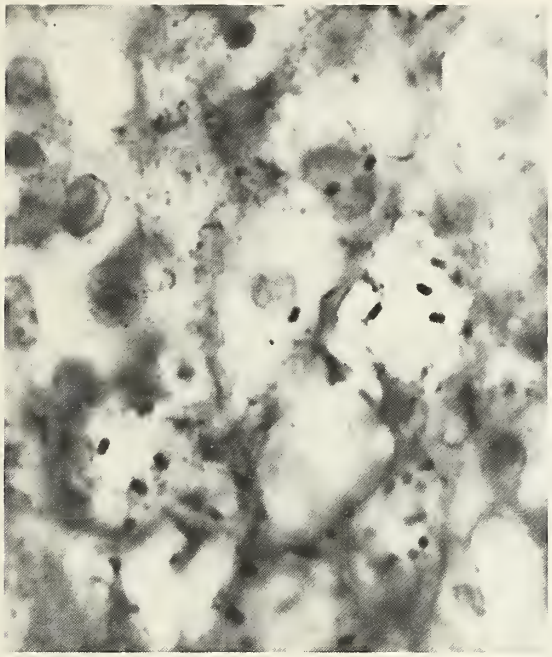

Figure 32
RHINOSCLEROMA
An oil immersion view of a Warthin-Starry stained section of the previous two slides histologically reveals a gram-negative bacilli within the Mikulicz cell cytoplasm, representing the Klebsiella rhinoscleromatis organism, the supposed causative agent. X1000.

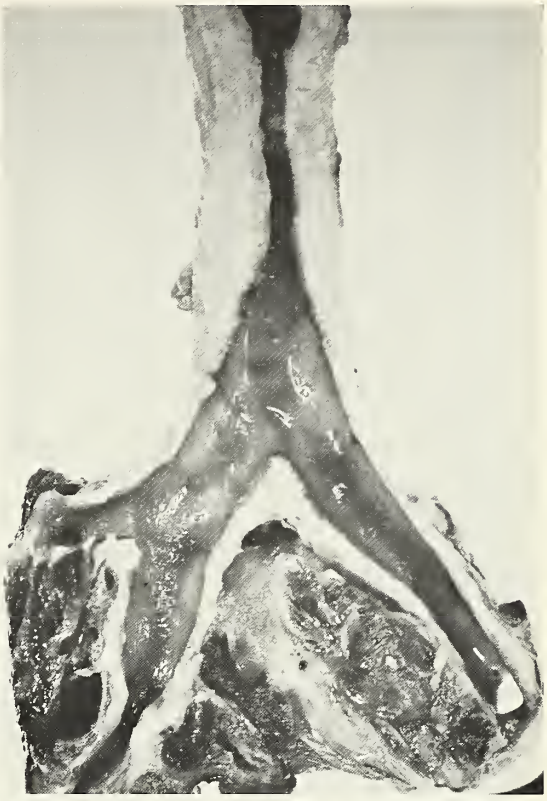

Figure 33
RHINOSCLEROMA
An autopsy specimen with a thickened trachea severely compromising the airway. The patient developed rhinoscleroma of the subglottic area and trachea following long-term involvement with the disease in the nasal cavity.

most commonly in those aged 20-35 years. The male to female ratio is 4 to 1 or greater. Some have suggested a relation to occupation with high exposure to dust, while others have related the spread to bathing or swimming in infected waters. Apparently the endospore organism enters the nasal cavity from water or dust and penetrates the mucosa. It then matures into sporangium in the nasal submucosal areas. These sporangium at maturity burst, spilling endospores into the submucosal tissue or the nasal cavity. The endospores may reinfect the local tissue or infect bathing areas or local environment through discharge via nasal drainage. The condition is also found in horses, cows, and mules. Transmission of infection among animals is thought to take place by contact with stagnant water in which infected animals have watered.

Gross. The lesion most commonly arises in the nasal cavity on the inferior turbinate of the lateral nasal wall. The nasal lesions may grossly resemble allergic polyps and are attached usually by a small delicate stalk. The polyps may be single or multiple, pedunculated or sessile. Minimal trauma may easily rupture the tissue, possibly causing a dissemination of the disease. The polyp surface will reveal small, pin-sized, yellow cysts incorporated within the mucosa (figs. 33, 34).

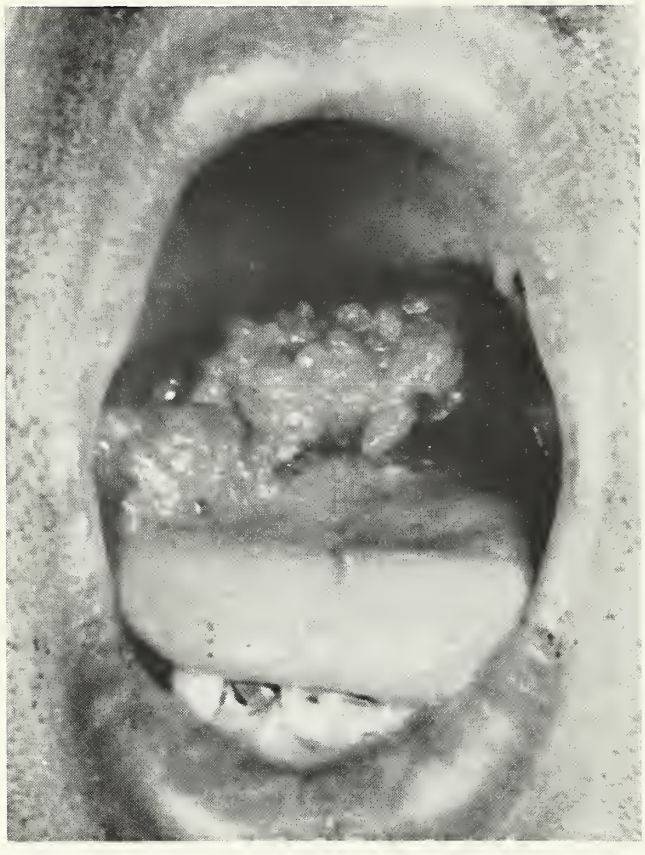

Figure 34
RHINOSPORIDIOSIS
An unusual presentation of rhinosporidiosis in an oriental male, in which the soft polypoid mass arose in the posterior nasal septum and presented through the choana into the oropharynx and oral cavity.

Microscopic. Pathologists should have no difficulty diagnosing rhinosporidiosis in hematoxylin-eosin stained preparations. The nasal lesion will reveal a thickened, even squamous metaplastic mucosa that together with the submucosal tissue will contain numerous globular cysts that range from 10 to 200 microns in diameter. These cystic structures, called sporangium, can contain several thousand endospores (figs. 35, 36). It is these endospores that are available to disperse the infection. The surrounding tissue reaction is a chronic inflammatory one, often with numbers of giant cells of the Langhans type (Khaleque).

Treatment. No drug has been reported to be effective in the treatment of rhinosporidiosis. Occasionally, spontaneous regression occurs. Treatment consists of surgical removal and repeated operations for recurrences as necessary.

Cholesterol Granuloma

This lesion nearly always arises as a result of hemorrhage in a confined space. Presumably, the lymphatic drainage is insufficient to remove completely the lipid components of the red cells that remain and become crystals of cholesterol and its esters. The human system regards these crystals as foreign bodies and reacts by the production of multinucleate giant cells and histiocytes. The intermixed cleftlike spaces represent the cholesterol crystals which have dissolved due to

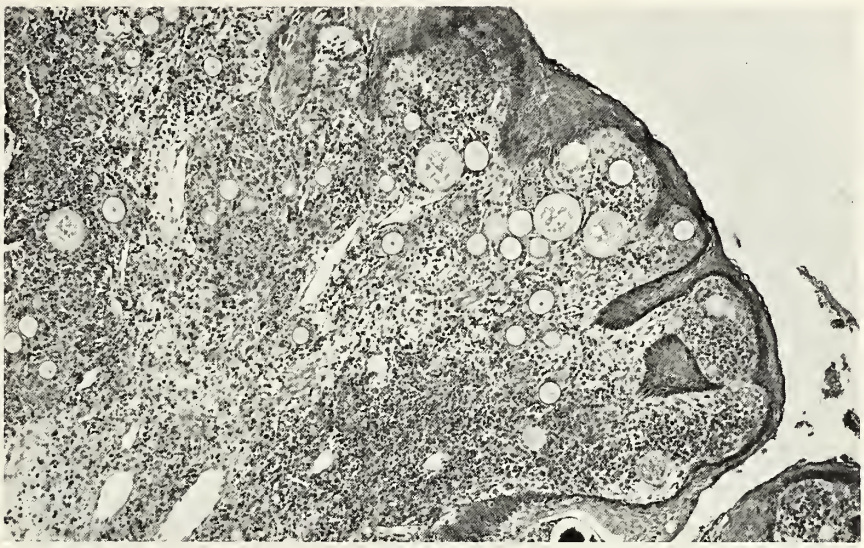

Figure 35
(Figures 35 and 36 are from the same patient)
RHINOSPORIDIOSIS

A soft, somewhat friable polyp arising from the lateral nasal cavity in an oriental adult male, diagnosed as rhinosporidiosis. The overlying mucosa consists of a prominent squamous cell metaplasia with an underlying severe chronic inflammatory infiltrate admixed with the sporangium of Rhinosporidium seeberi. X63.

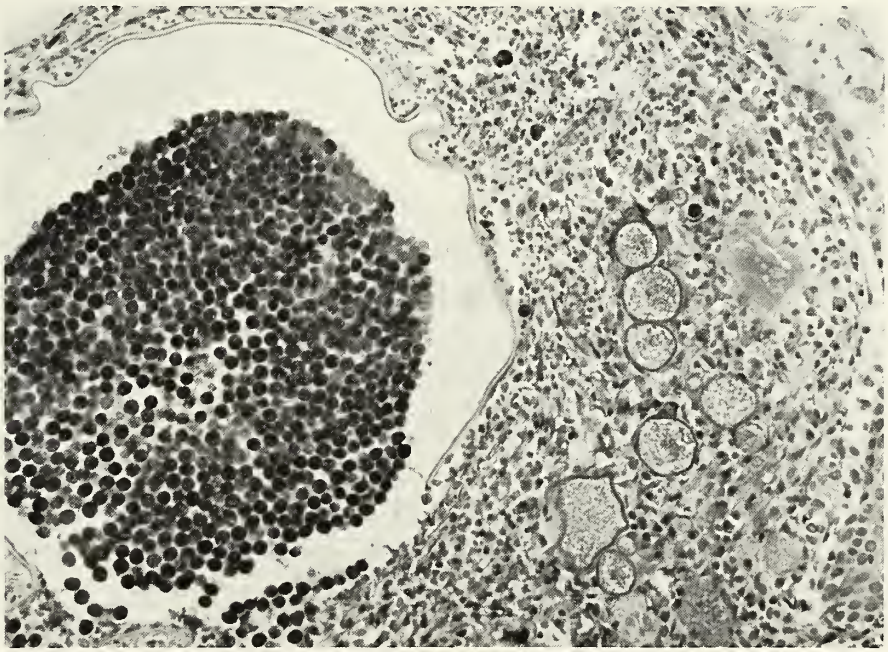

Figure 36
RHINOSPORIDIOSIS

High power magnification of figure 35 depicts a large sporangium with the double layered outside capsule of Rhinosporidium seeberi. The cavity contains endospores which can break out into the surrounding tissue, leading to the development of additional sporangia, such as are scattered throughout this illustration. X160.

the alcohol utilized in the fixation and staining procedures. The cholesterol granulomas are frequently found in the middle ear cleft and in thyroid adenomas. A lesion of the paranasal sinuses, usually the maxillary antrum, is encountered, in which clinical and radiologic evidence of sinus disease is suspicious of neoplasia. At surgical exploration the sinus is occupied by a submucosal blue mass beneath the mucosa, suggestive of a cyst. Histologic examination will reveal a submucosal granulation tissue containing blood, hemosiderin, and an extensive cholesterol granuloma. Surgical removal of the lesion usually offers a permanent cure.

There is a similar condition of the sinonasal tract that is referred to as rhinitis caseosa and is composed of a foul smelling discharge containing cholesterol crystals as well as acute and chronic inflammatory tissue. The sinuses involved may be lined by a keratinized layer of benign, stratified squamous epithelium. This latter condition has been referred to as cholesteatoma of the sinonasal tract. The etiology of this condition also appears related to trauma and hemorrhage in the anatomic area.

AMYLOID DEPOSITS

Amyloidosis, whether of primary or secondary type, is usually found to involve more than one internal organ. A solitary lesion of amyloid, giving rise to clinical symptoms and signs, is also noted in a variety of locations, such as the upper respiratory tract, urinary bladder, conjunctiva, and skin. Amyloid deposits in the upper respiratory tract appear to be the most frequent location of the solitary amyloid.

Incidence. In a series of 25 patients with amyloid of the upper respiratory tract in which the pathology was referred either to the AFIP or the Royal National Throat, Nose and Ear Hospital in London between 1960 and 1976, 13 patients were male and 12 were female. The age range was 19 to 90 years, with a median age of 41 years.

Site. Fifteen of the 25 patients with upper respiratory tract amyloid deposits revealed laryngeal ventricular fold involvement, mostly alone, but some ventricular fold deposits occurred together with pharynx, tongue, subglottic, tracheal, and bronchial lesions. In the 10 remaining patients there were either single localized or combined deposits in the nasal cavity, sinus cavity, tonsil, pharynx, subglottis, and trachea.

Natural History. The majority of patients with solitary focus of amyloid in the ventricular fold or elsewhere in the upper respiratory tract respond well to local endoscopic resection. There is usually a slow progressive increase in tumor mass. Involvement of trachea and bronchi presents more serious problems because of the narrowing of the airway, but even in these patients endoscopic resection controls the disease process until eventually the pathology becomes quiescent. Of the 25 patients in the above study, only one revealed extension of amyloid outside the upper respiratory tract, which occurred in the pyloric end of the stomach.

Gross. The affected area is focally swollen and may even by polypoid. The mucosal surface is smooth and may be bosselated (fig. 37). The cut surface does not reveal specific features.

Microscopic. The amyloid material is an eosinophilic, almost acellular material, prominently infiltrating the lamina propria of the upper respiratory tract. It always leaves intact the covering epithelium which is usually a pseudostratified columnar epithelium, but is occasionally a stratified squamous cell type (figs. 38, 39). A constant feature is the

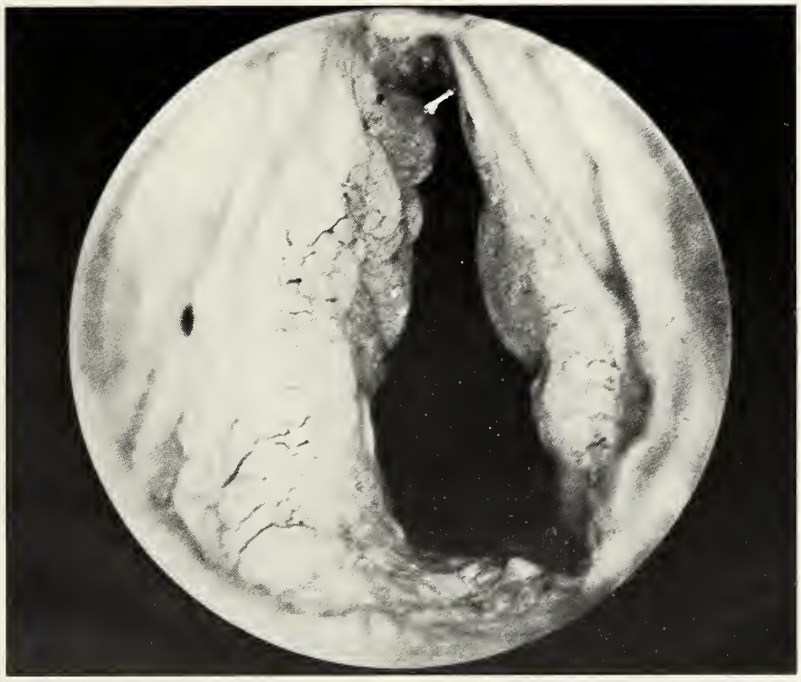

Figure 37
AMYLOIDOSIS

Primary localized amyloidosis in a 22 year old male with no evidence of disease elsewhere. Extensive amyloid tissue deposit on the left side of the larynx, with a similar but less marked process under the right cord, is evident. (Fig. 899 from Becker, W., Buckingham, R.A., Holinger, P.H., Korting, G.W., and Lederer, F.L. Atlas of Otorhinolaryngology and Bronchoesophagology. Philadelphia: W.B. Saunders Company, 1969.)

virtual disappearance of any mucoserous glands of the involved area. The amyloid may be deposited as thin flecks to large rounded masses of varying size. The latter may be observed as a replacement by amyloid of mucoserous gland lobules since all stages are seen in the pathologic process from partial involvement of individual acini to the final loss of all glandular structure. A foreign body giant cell reaction to the amyloid is frequent, as is a plasma cell infiltrate. Trabeculae of woven bone may permeate the amyloid material and an entrapment of cartilage fragments may be present, particularly in involvement of the trachea and bronchi. In the latter case, some resemblance to tracheopathia osteoplastica is present, but a study of histologic material from five patients with the latter disease did not reveal evidence of amyloid deposition (Michaels and Hyams).

TRACHEOPATHIA OSTEOCHONDROPLASTICA

In this condition, multiple endolumenal outgrowths of cartilage derived from the cartilages of the tracheal rings are present. Ossification of these growths is not unusual. The clinical picture is typically that of an older patient of either sex presenting with irregular, firm, bonelike protuberances beneath the mucosa of the trachea and bronchi (fig. 40). Occasionally, airway obstruction may ensue. The etiology is not established.

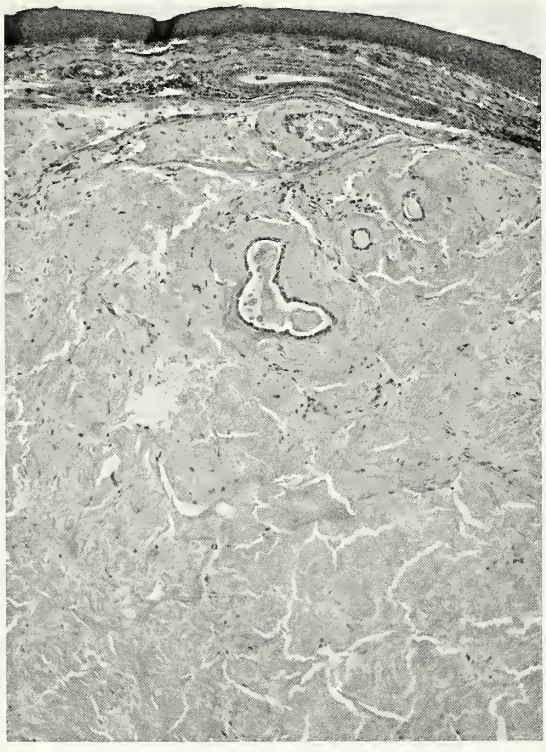

Figure 38
(Figures 38 and 39 are from the same patient)
AMYLOIDOSIS
This low power microscopic view of a raised tumor of the oropharynx reveals the amorphous deposit obliterating the subcutaneous tissue, including the seromucinous glands, which in this case remain only as atrophic ductlike structures surrounded by amyloid. X63.

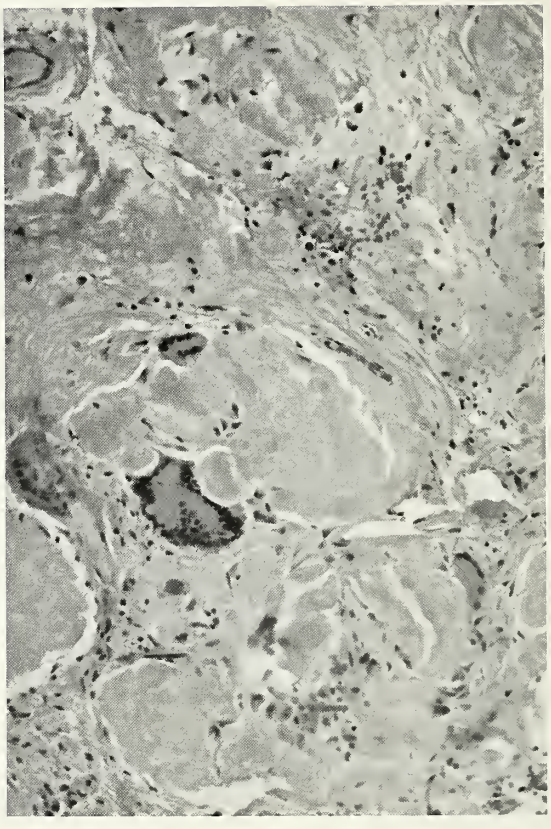

Figure 39
AMYLOIDOSIS
Higher magnification of the previous illustration shows the foreign body cell reaction to the amyloid. X160.

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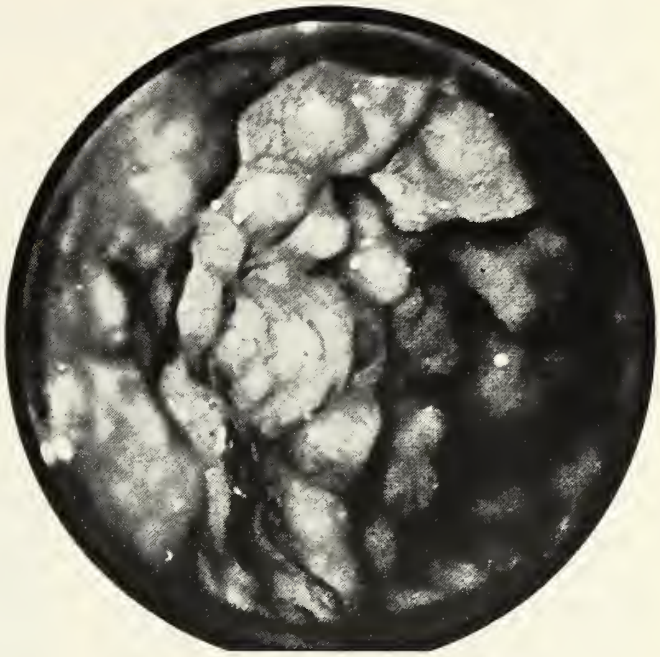

Figure 40
TRACHEOPATHIA OSTEOCHRONDROPLASTICA
The left lateral, anterior, and right lateral walls of the trachea of a 37 year old woman who complained of cough, dyspnea, and occasional hemoptysis. Clinical and histologic diagnosis was tracheopathia osteochrondroplastica. (Fig. 953 from Becker, W., Buckingham, R.A., Holinger, P.H., Korting, G.W., and Lederer, F.L. Atlas of Otorhinolaryngology and Bronchoesophagology. Philadelphia: W.B. Saunders Company, 1969.)

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PAPILLOMA OF THE UPPER RESPIRATORY TRACT

Papillomas by definition are benign, exophytic, epithelial neoplastic proliferations arising from a cellular surface or mucosa. In the upper respiratory tract, they may occur anywhere from the nostrils to the trachea and their clinicopathologic implications will vary from one anatomic area to another.

PAPILLOMA OF THE NASAL VESTIBULE AND NOSTRILS

This area is emphasized because, in comparison with those arising in the sinonasal tract, papillomas of the vestibule and nostril behave essentially as benign, squamous papillomatous neoplasia (verruca vulgaris, warts, digitate verruca) arising anywhere on the skin surface (fig. 41). Rarely do they recur after simple removal and malignant transformation is not a problem.

PAPILLOMA OF THE SINONASAL TRACT

SYNONYMS AND RELATED TERMS: Inverted papilloma; schneiderian papilloma; transitional cell papilloma; papillary sinusitis; Ewing's papilloma; cylindrical cell papilloma; Ringertz papilloma; papillary adenoma; mucocystic papillary adenoma.

Definition. Papilloma of the sinonasal tract is a benign, exophytic, neoplastic proliferation arising from the sinonasal tract respiratory (schneiderian) mucosa, consisting of an epithelial component of either squamous or tall columnar epithelium, or both, and usually admixed with varying amounts of mucous cells or mucous pools. The mesenchymal stroma may be myxomatous and voluminous or a distinctive, scanty, vascular, fibrous core such as is seen in the exophytic septal type.

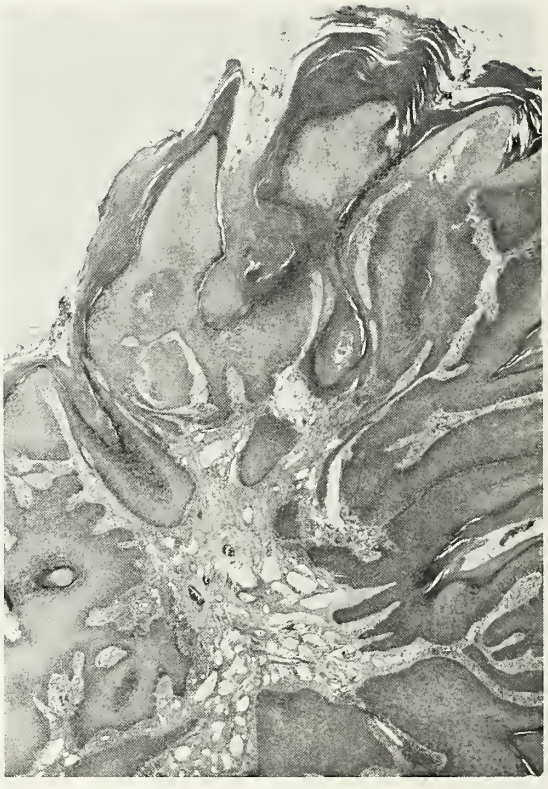


Figure 41
PAPILLOMA
An exophytic, keratinizing, squamous cell papilloma of the anterior vestibule of the nose. X25.

Frequency and Age. Papillomas are by far the most common benign epithelial neoplasms of the sinonasal tract contained in the AFIP-OTR material, comprising over 500 cases and about 10 percent of all neoplasia, benign and malignant, of the anatomic area. Literature reports vary from .4 to 4.7 percent of all sinonasal tract neoplasia (Hyams). The median age in the AFIP-OTR cases was 35 years, with a range from 11 to 85 years; however, sinonasal tract papillomas were rare under 21 years of age (fig. 42). Septal papillomas appear to occur at a younger age than

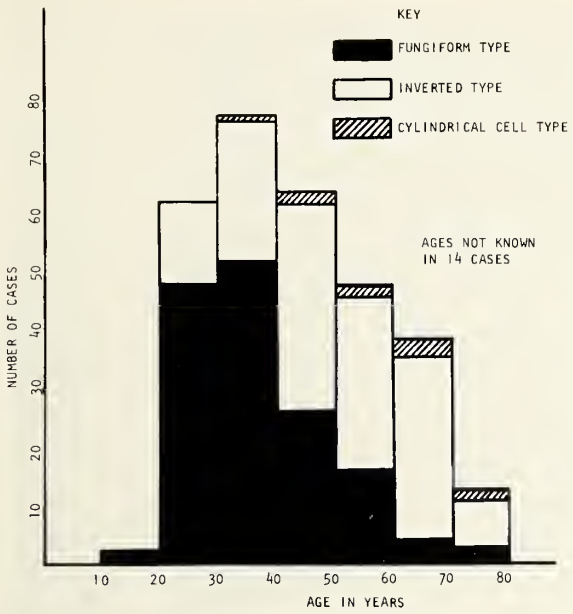


Figure 42
PAPILLOMA
This chart represents the ages in 322 cases of sinonasal tract papillomas from the AFIP Tumor Registry. Note the virtual absence of the neoplasm in the pediatric population.

do lateral nasal wall and/or paranasal sinus papillomas. Males predominate over females 5 to 1. Caucasians are in the great majority.

Histogenesis. The cause of sinonasal papilloma is obscure. Viral etiology seems unlikely, particularly since papillomas rarely occur in the pediatric age group and there is no micromorphologic evidence to support such an etiology (Jahnke; Gaito et al.). No relationship with the environment, work-related exposure, or personal habits has been implicated in humans (Lasser et al.). Herrold reported papillomas that were produced in the anterior nasal cavity of Syrian hamsters by dimethylnitrosamine administered intraperitoneally and topically on the skin surface. The available histology leaves some doubt as to whether these experimental tumors were not carcinomas rather than papillomas. There has been a tendency to consider chronic inflammations, particularly sinonasal polyposis, to be forerunners of papillomas; however, Hyams' study of 315 cases of sinonasal tract papillomas found only 2 patients with a history of previous chronic sinonasal inflammation and 1 additional patient who had previous inflammatory polyps removed (no histology recorded). Calcaterra and associates, in 34 patients, could not elicit a history of upper respiratory allergy or previous inflammatory polypectomy. The histology of the sinonasal papillomas supports origin from the respiratory (schneiderian) mucosa and not from mucoserous glands or other structures. There is no significant reported occurrence of sinonasal papillomas with concurrent papillomas of other areas of the upper respiratory tract or other areas of the body.

Clinical. The symptoms vary with the location of the papilloma in the sinonasal cavity. Half the lesions in patients reported by Hyams arose from the lateral nasal wall and/or the paranasal sinuses and were usually quite bulky, causing mainly obstructive symptoms. In this particular half, 20 percent were recorded as present only in the nasal cavity, 40 percent involved solely the paranasal sinuses, and the remaining 40 percent involved mutually the nasal cavity and paranasal sinuses. When the paranasal sinuses are involved with papillomas, it is the maxillary antrum that is implicated in over 75 percent of patients. However, the remaining paranasal sinuses, especially the ethmoid group, may originate the tumor. Combinations of different sinus involvement, with or without implicating the nasal cavity, is not unusual. In the remaining half of Hyams' series of patients with sinonasal tract papillomas, the tumors arose from the nasal septum and appeared grossly as flat and wart-

like, usually producing epistaxis initially. In many cases, these septal papillomas were asymptomatic tumors found on routine examination. Pain was a rare complaint, especially with septal papillomas. Most clinical presentations were unilateral, with only a rare case occurring bilaterally. Papillomas may arise primarily from the nasal floor or roof, but usually involvement of these areas is an extension of the tumor from the lateral nasal wall.

When a patient presents with multiple papillomas of the nasal cavity and/or paranasal sinuses, the possibility exists for origin from multiple foci, although as one may observe later in the microscopic description, the papilloma has a tendency to creep along adjacent mucosal surfaces and could possibly, by this route, disseminate the neoplasm to other areas of the sinonasal tract.

The most common complication with sinonasal tract papilloma is recurrence following removal. This problem occurs in 40 to 60 percent of patients in published series, whether the papillomas involve the lateral nasal wall, paranasal sinuses, or nasal septum (Hyams). Malignant transformation is the next most common clinical complication and is estimated in incidences of 7 to 53 percent in published reports (Yamaguchi et al.). Hyams, in the 315 cases from the AFIP-OTR material noted a 13 percent incidence of carcinomatous transformation or concurrent malignancy. The consultative nature of the AFIP material would tend to support a lower real incidence among the general population, perhaps between 5 and 10 percent. Of interest is that no nasal septal papilloma in the AFIP-OTR material has demonstrated any malignant transformation nor been associated with a concomitant septal malignancy. The majority of malignant complications occurred in patients over 50 years of age and did not prove to be related to papilloma recurrence.

Although histologically benign papillomas, on rare occasions, may cause bone displacement or destruction and facial deformity (Hyams; Myers et al.), particularly when involving the paranasal sinuses (fig. 43), such symptoms should lead to the suspicion of a malignant neoplastic process or a malignant transformation in a previously benign papilloma. In such a patient, it is wise to submit all surgically removed material for microscopic examination in order not to overlook the possible minute malignant focus.

Common diagnostic radiologic appearance is a unilateral mass in the nasal fossa with opacification of the contiguous maxillary sinus in a moderately advanced tumor stage; however, other radiologic patterns may be encountered and it is therefore impossible to categorize any of these findings as specific for sinonasal tract papillomas (Momose et al.).

Gross. Papillomas originating from the lateral nasal walls and/or paranasal sinuses most often present a bulky, polypoid or bosselated, rubbery, firm, nontranslucent, gray to pink lesion, capable of filling the nasal cavity and/or the paranasal sinuses. Occasionally, a ragged, beefy, papillary surface of the tumor is described. The tumor may be quite vascular, leading to significant hemorrhage at removal. Papillomas arising from the lateral nasal wall and/or paranasal sinuses appeared to arise from the mucosa by a broad base, while those originating from the nasal septum and, rarely, from the posterior turbinate area, present a flattened cauliflower or raspberry pink appearance, attached to the mucosal surface by a narrowed stalk (fig. 44).

Microscopic. Some investigators are disposed to classify sinonasal tract papillomas micromorphologically as an inverted type, as

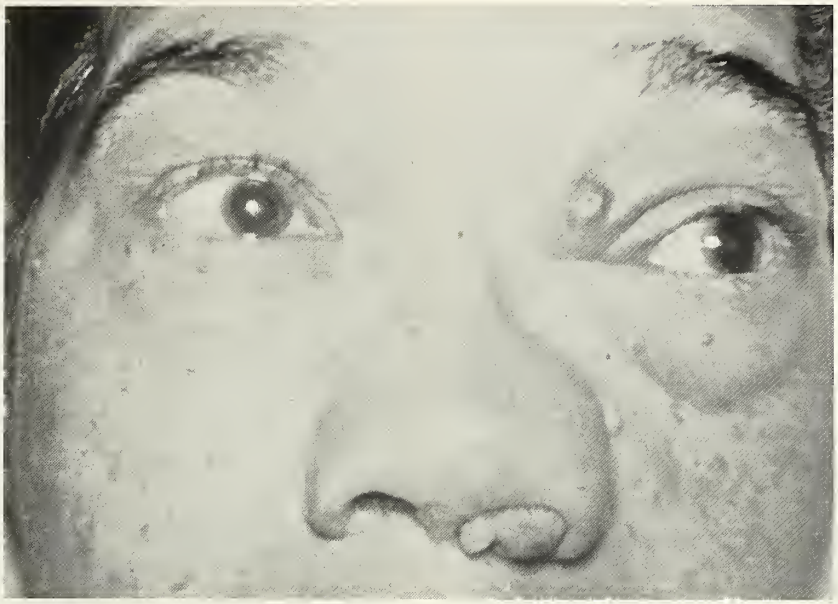


Figure 43
PAPILLOMA

A clinical picture of an inverted type papilloma associated with proptosis, protruding from the nose. The histologically benign papillomatosis involving the left sinonasal area caused pressure erosion of the frontal sinus bony wall and invaded the cranial cavity. (Fig. 1a from Myers, E.N., Schramm, V.L., Jr., and Barnes, E.L., Jr. Management of inverted papilloma of the nose and paranasal sinuses. Laryngoscope 91:2071-2084, 1981.)

Figure 44
PAPILLOMA

A gross specimen of a papillomatous mass arising from the lateral nasal wall in a 45 year old man.

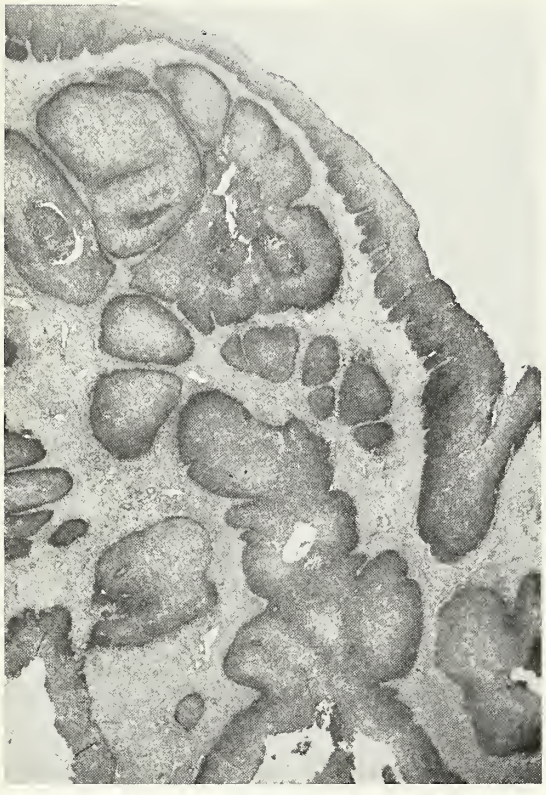


Figure 45
PAPILLOMA
The typical histologic appearance of epithelial papilloma of the lateral nasal wall and/or paranasal sinus cavities, with the so-called inverted architecture. X25.

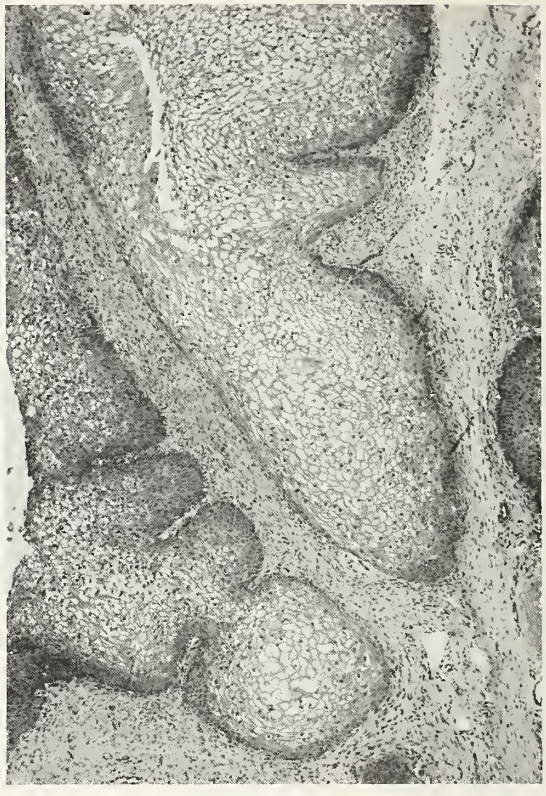


Figure 46
PAPILLOMA
A papilloma of the sinonasal tract lateral nasal wall and/or paranasal sinuses reveals the occasional clear cell histology of the epithelial neoplastic element. This is a benign pattern with abundant glycogen content in the cells. X63.

well as a fungiform, cylindrical, or transitional cell histologic type. This classification has caused confusion, even though there may be clinicopathologic characteristics related to the particular anatomic area of origin of the papilloma. The simple designation of all sinonasal tract papillomas, regardless of point of origin, gross configuration, and histologic pattern as papillomas of the sinonasal tract is suggested as the most simple and uncomplicated designation. In those papillomas arising from the lateral nasal wall and/or paranasal sinuses, the epithelial neoplastic component will consist of a uniform epidermoid (transitional) cell (figs. 45-47), or, less often, a pseudostratified cylindrical (columnar) cell (figs. 48-50), or even, occasionally, combinations of basal epidermoid cells with a surface layer of a columnar, pseudostratified, respiratory type cell (fig. 51). Barnes and Bedetti preferred to consider the papilloma exhibiting the pseudostratified cylindrical (columnar) cell as an oncocytic schneiderian papilloma. They demonstrated a morphology that supported a relationship of this cell to the oncocyte, but clinically this did not change previous conceptions of the behavior of this particular type of papilloma. The epidermoid cells that make up a papilloma may reveal typical "prickles," particularly in

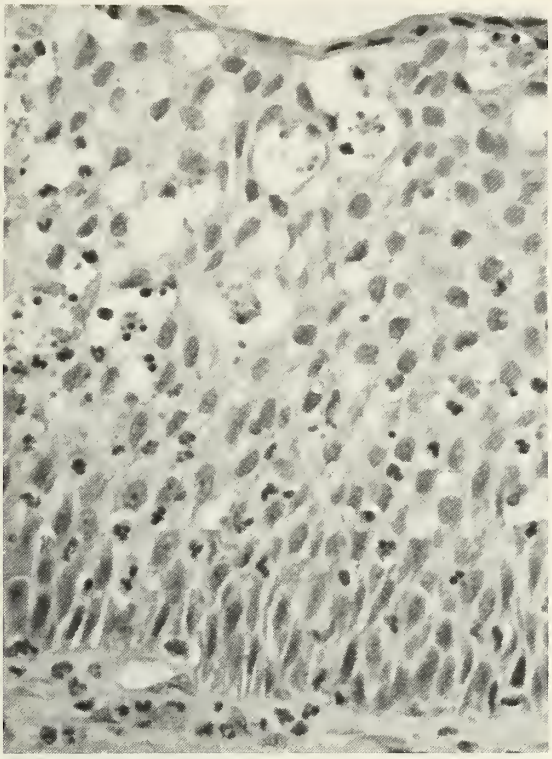


Figure 47
PAPILLOMA
High magnification of a papilloma of the sinonasal tract lateral nasal wall and/or paranasal sinus cavity emphasizing the squamoid micromorphology and intercellular bridges in the basal area. X400.

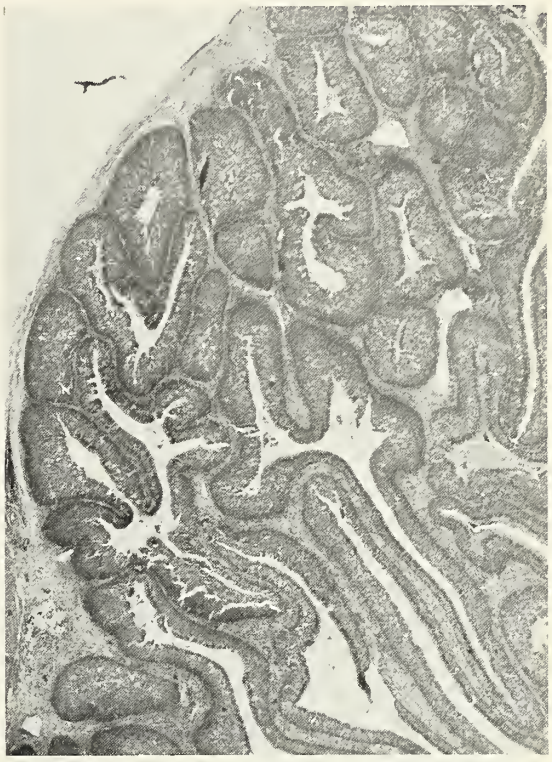


Figure 48
PAPILLOMA
A papilloma of the lateral nasal wall and/or paranasal sinus cavities with an "inverted" architectural pattern and tall columnar epithelial cells forming the neoplastic element. X25.

inner basal layers, or they may have the elongated transitional cell appearance. Not infrequently, the epidermoid (squamous) cell neoplastic element may reveal, in part, a vacuolated, glycogen-filled, benign squamous cell. Cilia may be noted on the outer surface of the cylindrical cell tumor component (fig. 50). Nuclei vary from vesicular to round, with a uniform dark chromatin, and seldom exhibit a distinct nucleolus. Prominent nuclear uniformity and polarity is consistent throughout, with occasional benign mitotic figures, but never sufficient cellular atypia or mitotic activity to suggest anaplasia. Varying amounts of mucous cells or mucous pools are frequently intermixed with the epithelial element. Surface keratin or any form of dyskeratosis is unusual in any benign sinonasal papilloma and its presence should alert the examiner to the possibility of either a well differentiated squamous cell carcinoma, a verrucous carcinoma, or a malignant degeneration of a papilloma. In 26 of the AFIP-OTR's 315 cases of sinonasal tract papillomas that contained surface keratosis (fig. 52), 14 demonstrated an associated squamous cell carcinoma. However, desquamation of surface epithelium was quite common, with no serious implications.

In papillomas arising from the lateral nasal wall and/or paranasal sinuses, the stroma is usually of moderately vascular myxomatous

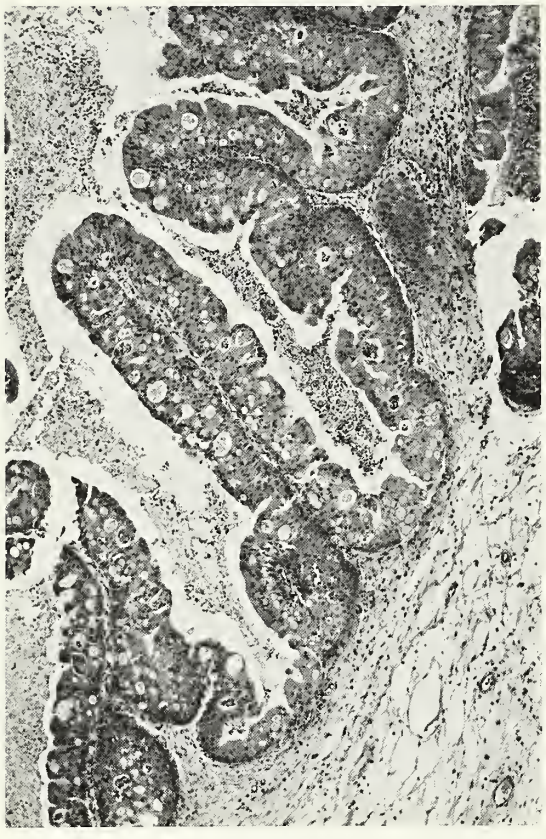


Figure 49
PAPILLOMA
In this papilloma, similar to that depicted in the previous illustration, the presence of tall columnar neoplastic cells have led to the designation of "cylindrical" cell type papilloma. Numerous mucous cysts are also seen. X63.

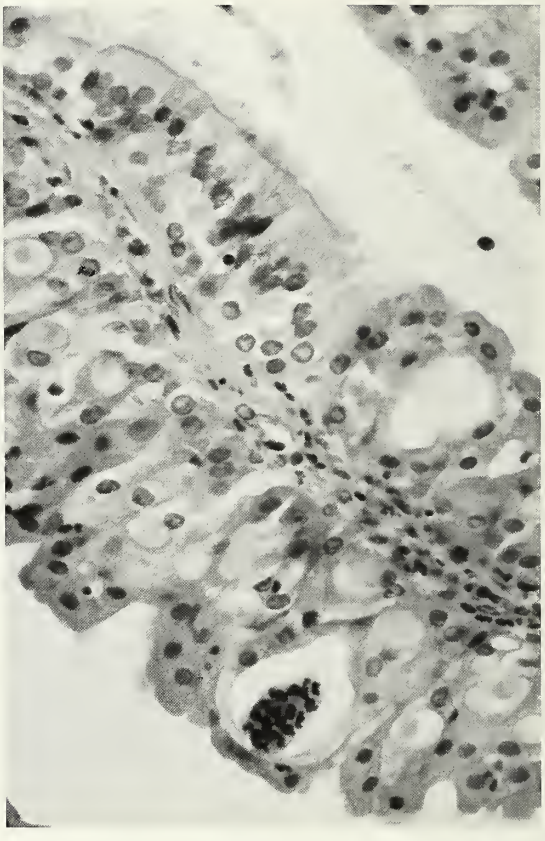


Figure 50
PAPILLOMA
Note cylindrical or columnar neoplastic cells and cilia on some surfaces. The cystlike inclusions represent apparently distended mucous cells and have been mistaken for the rhinosporidiosis organism. X400.

fibromatous tissue mainly devoid of glandular structures. In such papillomas, it is quite often the predominant feature, but can vary in amount. The stromal structure of the lateral nasal and/or paranasal sinus papillomas is histologically reminiscent of that of the inflammatory polyp, and it is so interrelated with the epithelial neoplastic element as to suggest an "inversion" of the latter into the stroma. Papillomas arising from the septum have a similar epidermoid (transitional) cell element, but do not contain a cylindrical (columnar) cell element (fig. 53). Mucous cells or mucous pools are usually seen. The stroma in the septal papilloma is a thin, fibrovascular connective tissue central core and does not support the so-called inverted architecture common in those papillomas arising from the lateral nasal wall and/or paranasal sinuses. Throughout the above-described papillomas, varying collections of inflammatory cells may be noted within the epithelial and/or stromal area. The inflammatory cell may be acute, chronic, or allergic in nature, or a mixture of all. The infiltration might be intense in any area of the papilloma,

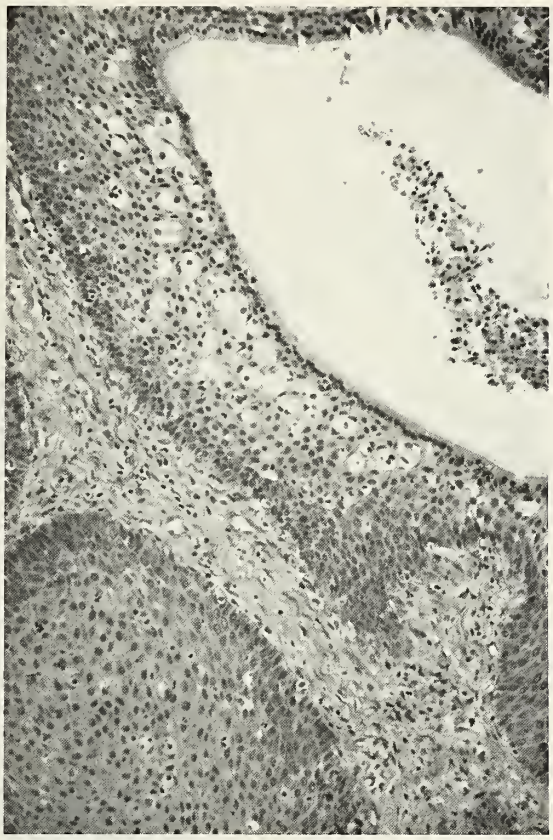


Figure 51
PAPILLOMA
In this lateral nasal wall and/or paranasal sinus cavity papilloma, there is an admixture of both the epidermoid and columnar or cylindrical cell neoplastic element. X63.

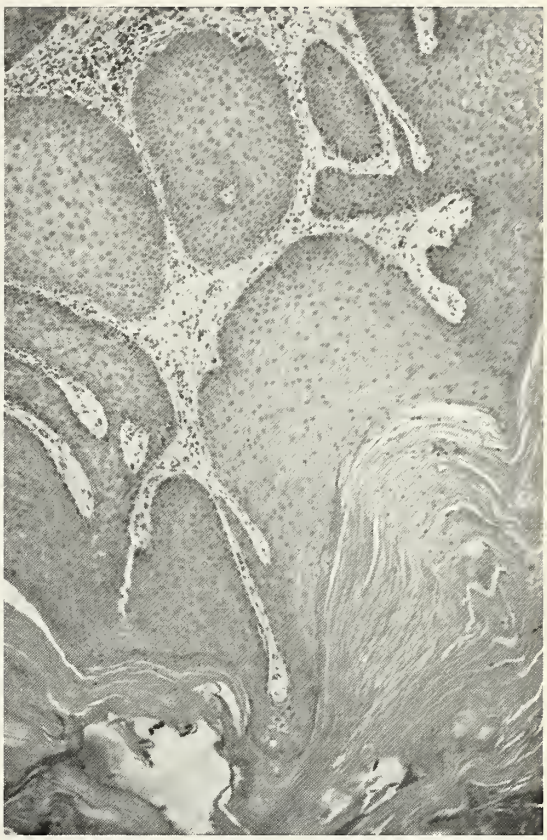


Figure 52
PAPILLOMA
There is marked keratosis of the surface of this sinonasal tract papilloma. This is a rare occurrence and the possibility of the lesion representing a well differentiated squamous cell carcinoma or a verrucous carcinoma must be ruled out. X160.

while absent in other parts of the same tumor. In the AFIP-OTR material, no prognostic significance was placed on the inflammatory cell infiltrate.

To explain the recurrences of sinonasal tract papillomas, the histologic evidence supports a spreading of histologically benign epidermoid metaplasia for varying distances along the surfaces adjacent to the papilloma (fig. 54). If these extensions are not surgically removed, they could be a nidus for recurrence. Also, this benign surface metaplasia should explain the mode of spread to various sites of involvement in the sinonasal tract, even via the narrow sinus ostia.

In malignant cases, there should be demonstrated a benign papillomatous structure, together with carcinoma of a keratinizing or nonkeratinizing squamous cell variety. Most often, a transition (Schiller's line) from the benign to the malignant epithelial neoplasia is noted (fig. 55), but the possibility of an independent second primary carcinoma cannot be excluded in some cases of sinonasal tract papilloma with concomitant carcinoma. There were 12 patients in the AFIP-

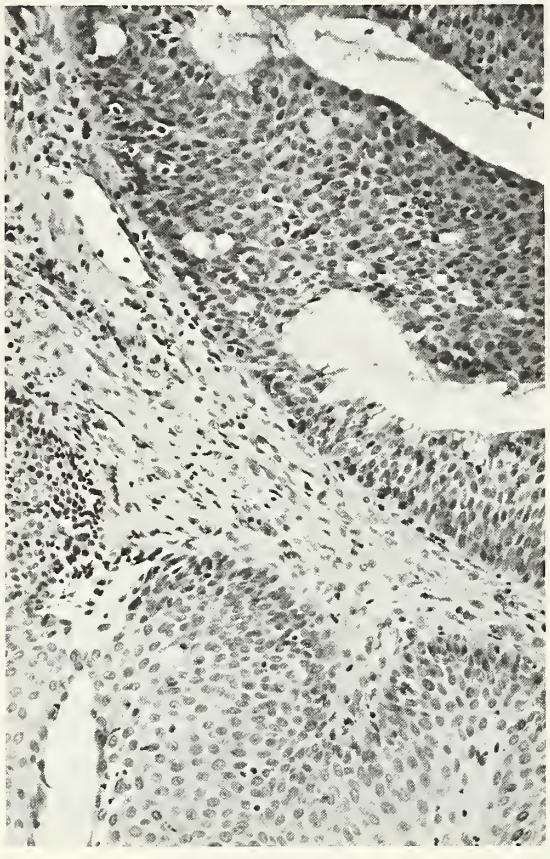


Figure 53
PAPILLOMA
This emphasizes the benign epidermoid morphology and mucous cells in nasal septal papillomas. X160.

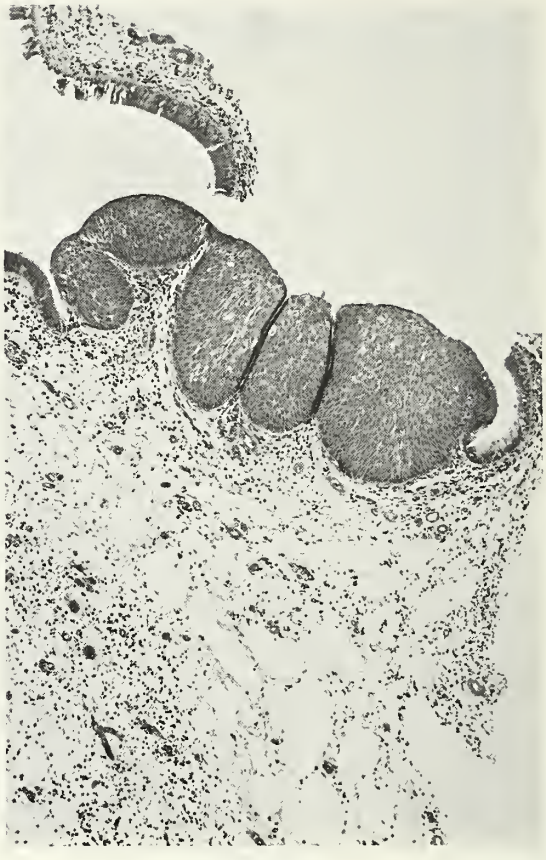


Figure 54
PAPILLOMA
Papillomas of the sinonasal tract tend to extend along the mucosal surface and involve adjacent sinonasal cavities. They may remain following surgical removal, leading to a recurrence. X63.

OTR material with in situ carcinoma in an otherwise benign clinical and histologic papilloma arising from the lateral nasal wall and/or paranasal sinuses. Since these patients produced no clinical evidence of destruction, all were treated surgically as benign papillomas and, on long-term followup, only one case recurred, demonstrating an aggressive malignant behavior.

The ultrastructural studies (Gaito et al.; Jahnke) reveal a characteristic polygonal cell demonstrating the usually cytoplasmic features of a stratified squamous cell type resting on a basement membrane. Occasionally, particularly on papillomas of the lateral nasal wall or paranasal sinuses, surface cells might be typical ciliated columnar epithelium. No surface keratin or keratohyalin granules were demonstrated. Goblet cells could be identified. No conclusive viral particles were seen. Immunoperoxidase studies to demonstrate keratin should be positive.

Differential Diagnosis. A prominent and unfortunately distressing problem is the mistaken histologic diagnosis of respiratory carcinoma of the sinonasal tract as papilloma.

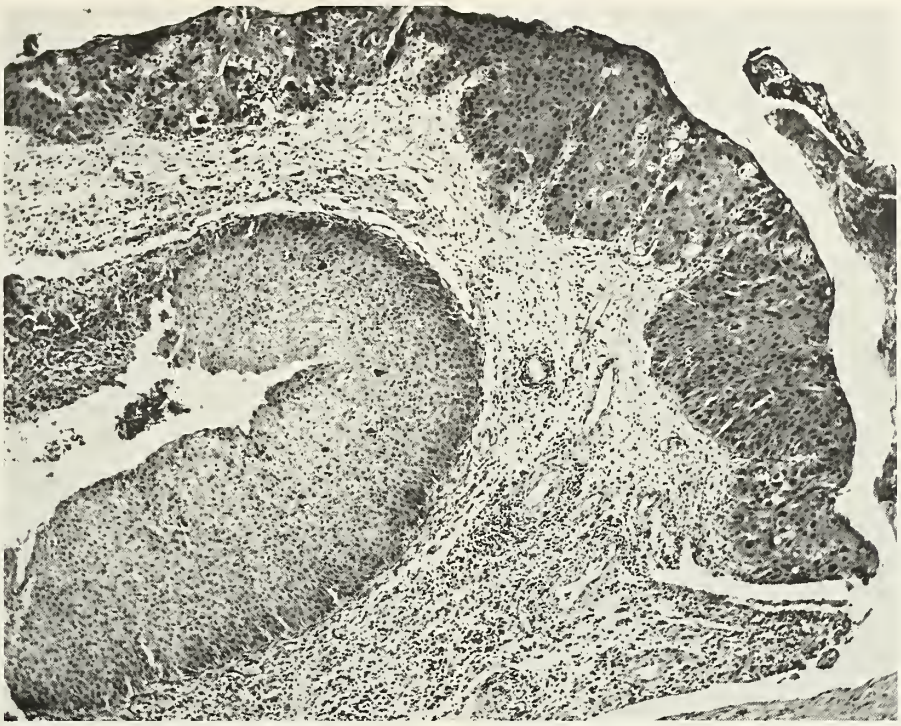


Figure 55
PAPILLOMA AND CARCINOMA
A papilloma of the lateral nasal wall and/or paranasal sinus cavity is seen in the left of this photomicrograph. The surface on the right contains a squamous cell carcinoma, interpreted as a malignant transition from the papilloma. X63.

In the AFIP-OTR material there are some 40 patients with an aggressive malignant process occurring in tumors initially diagnosed histologically as papillomas. All have since been proved to be de novo carcinomas arising from the respiratory mucosa and with no histologic support for a concomitant papilloma (figs. 56, 57). Carcinomas of the sinonasal tract may well demonstrate a so-called inverted microarchitecture, but the epithelium is malignant, with all the typical anaplasia and mitosis necessary for the correct histologic diagnosis.

Occasionally, squamous metaplasia on the surface mucosa is seen in chronic inflammatory polyposis of the sinonasal tract and raises the question of papilloma (fig. 11). If the stratified squamous epithelium is more than a dozen cell layers thick and shows the prominent "inversion" into underlying stroma, the lesion is more than likely a sinonasal papilloma.

Metastasis. Metastasis of the histologically benign papilloma of the sinonasal tract should not occur. A case report by Schoub and associates supported metastasis of a nasal cavity papilloma to a cervical lymph node. The available illustrated histologic evidence did not rule out a primary nasal cavity respiratory mucosal carcinoma with regional node metastasis or, possibly, the occurrence of a metastatic carcinoma to the cervical lymph node from a secondary primary, such as an occult upper respiratory tract site.

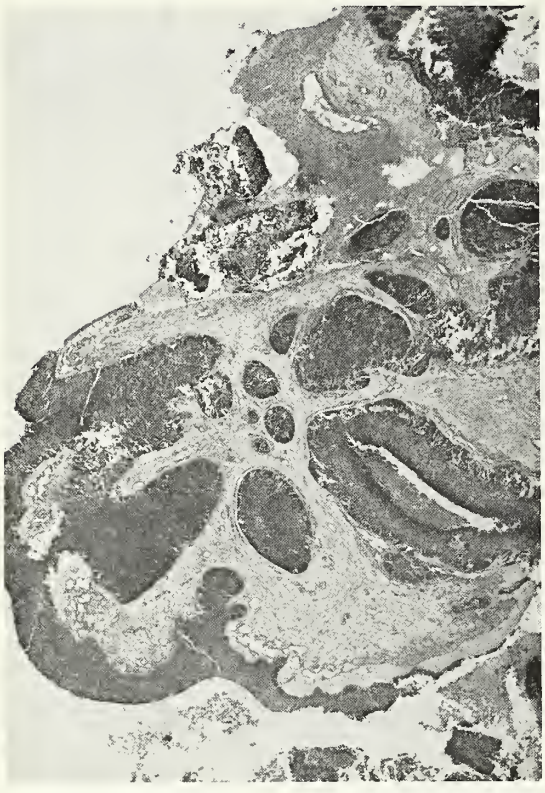


Figure 56
(Figures 56 and 57 are from the same patient)
CARCINOMA
This destructive sinonasal tract lesion was erroneously diagnosed as an "inverting" papilloma. Mucosal carcinomas that arise de novo can simulate an inverted architecture. X25.

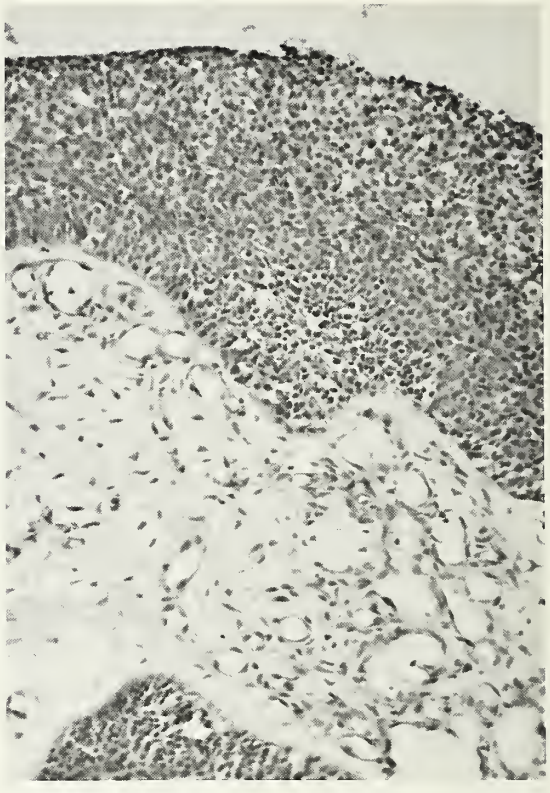


Figure 57
CARCINOMA
Higher magnification of the previous illustration confirms the dysplastic histology of the neoplastic epithelium. X160.

Treatment. An assured complete surgical removal is the treatment of choice (Batsakis). The intranasal removal by loops, snares, or simple excision invites recurrence. Mutilating surgery does not appear warranted for the treatment of a histologically benign papilloma, but an aggressive surgical approach with good exposure, including the removal of an encompassing zone of uninvolved tissue, is necessary for the successful assured complete removal of the neoplasm (Suh et al.). Radiation or chemotherapy has no reported benefit in the therapy of sinonasal papilloma.

Prognosis. With adequate surgical excision, the prognosis is optimistic. Inadequate surgery invites unlimited possibilities of recurrence and, in the older patient, the possibility of the development of a concomitant carcinoma is increased. The over 50 percent incidence of the malignant complication recorded by Yamaguchi and associates appears much too high, while the 7 percent incidence of Suh and co-workers is more in line with the overall experience of the literature and the AFIP-OTR.

PAPILLOMA OF THE NASOPHARYNX AND PHARYNX

Papillomas arising from the nasopharynx are uncommon and the 12 patients in the AFIP-OTR material each presented a gross bulky, firm mass which histologically consisted of a proliferative, uniform, histologically benign, squamous epithelial neoplasia. There was supporting histologic suggestion of an inversion of the epithelial proliferation into a scanty underlying fibrous stroma simulating the so-called inverted papilloma of the lateral nasal wall and/or paranasal sinus (figs. 58, 59) (Nosanckuk). After simple surgical removal, there was no recurrence and no evidence of possible association with developing carcinoma in the AFIP-OTR experience. Geshickter noted that embryologically the ectodermally derived schneiderian sinonasal mucosa could, and probably did, extend posteriorly beyond the choana into the nasopharynx, which could be an accepted explanation of the unusual morphology of nasopharyngeal papilloma. The oropharynx and hypopharynx occasionally reveal the typical exophytic, narrow stalked, finely lobulated, gray papilloma, which responds to simple removal with only rare complications of recurrence or associated malignancy.

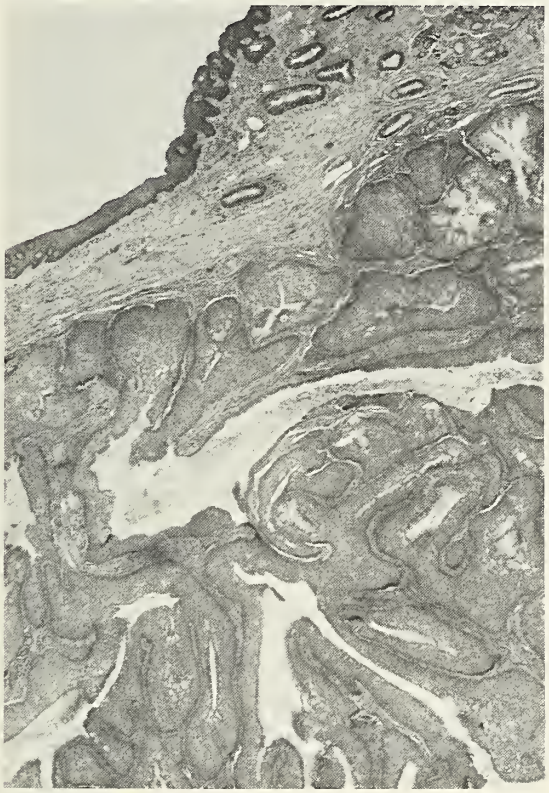


Figure 58
(Figures 58 and 59 are from the same patient)
PAPILLOMA
This is a rare papilloma of the nasopharynx and pharynx. In the nasopharynx, particularly, the papilloma retains the inverting characteristic seen in the sinonasal papilloma. X25.

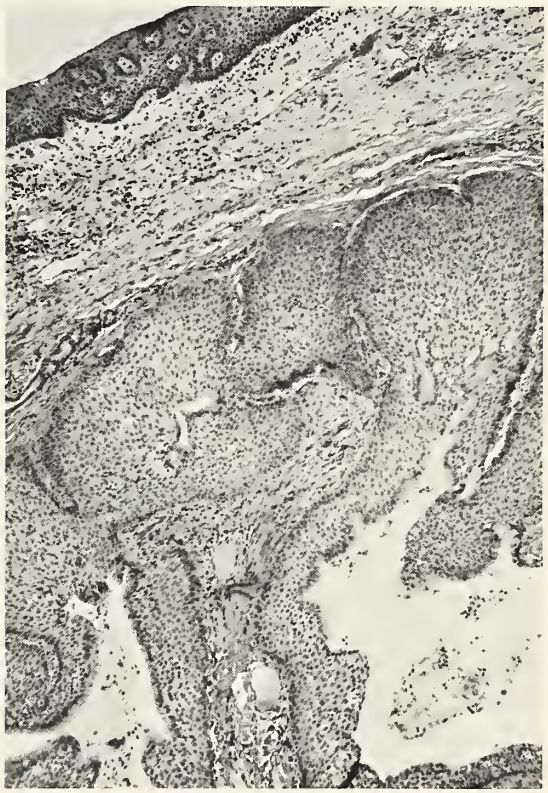


Figure 59
PAPILLOMA
Higher magnification of the previous illustration emphasizes the inverted architecture. Perhaps the schneiderian sinonasal tract mucosa can extend into the nasopharynx, giving rise to this type of papilloma. X160.

PAPILLOMA OF THE LARYNX AND TRACHEA

SYNONYMS AND RELATED TERMS: Juvenile papillomatosis; florid laryngeal papillomatosis of the adult.

Definition. A laryngeal or tracheal papilloma is a histologically benign, exophytic neoplastic growth with branching fronds of squamous epithelium and a central fibrous tissue stromal core. Attachment to the larynx or trachea is usually by a narrow stalk covered by squamous epithelium; however, a wide area of continuity with the mucosal surface may occur. Surface hyperkeratosis is rare.

Papillomas of the larynx and trachea, all of squamous cell type, are the most common benign neoplasm of this anatomic area. There is a tendency to divide these laryngeal papillomas into juvenile and adult types and, even though there are unique clinical characteristics of papillomas of both age groups, they will be discussed together. Papillomas may involve the trachea initially, however most tracheal involvement is a result of spread from the larynx.

Frequency and Age. Squamous papillomas account for approximately 10 percent of all neoplasms in the larynx and trachea in the AFIP-OTR material. In Holinger and associates' 109 cases, half were of juvenile (under 16 years of age) onset. Over half the juvenile onset papillomas (32 patients) were diagnosed before the age of 5 years, the youngest being 1 month. The oldest age of onset in their series was 72 years. The sex distribution was equal and there was no racial predilection. There has been an indication that, particulary in the juvenile onset laryngeal papillomas, the patients are mainly from a low socioeconomic level (Szpunar).

Etiology and Histogenesis. There is a consensus of the medical literature that the laryngeal and tracheal papillomas, regardless of age of onset, are virus induced. Ullmann was successful in self-inoculating a laryngeal papilloma filtrate into the skin of his arm. No etiologic virus has been cultured; however, Boyle and associates felt they could identify ultrastructurally the Papova virus in laryngeal papillomas of both pediatric and adult onset. The development of the peroxidase-antiperoxidase test technic has led Braun and associates to detect papilloma virus antigen in 7 of 15 patients with juvenile onset laryngeal papillomas, but only with a questionable demonstration in adult onset laryngeal papillomas. Many have observed the occurrence of condylomata acuminatum in the maternal genitalia at the time of parturition of children who later developed laryngeal papillomas (Quick et al., 1980). This data strongly supports a viral etiology in at least the juvenile onset papillomas of the larynx.

Clinical and Gross. Regardless of the age of onset, changes of phonation usually occur first, with progressive hoarseness or huskiness and, finally, aphonia. Possible respiratory changes are croupy cough, stridor, dyspnea, cyanosis, or perhaps asphyxia. In long-term involvement, children may develop a funnel breast due to the need of using accessory muscles of respiration. Personality changes in children are not unusual, because of the forced limitation of their activity. Grossly, the papillomas are glistening, elevated, mulberry-like, nodular, white to pink masses and may initially occur anywhere within the larynx, but chiefly on the true vocal cords, anterior commissure, and the ventricular folds (false cords) (fig. 60). Initially they may be single or multiple lesions, varying in size from small nodules to sessile plaques or large nodular masses with a diameter of up to 2.5 cm. The tumors are usually friable and bleed easily with slight

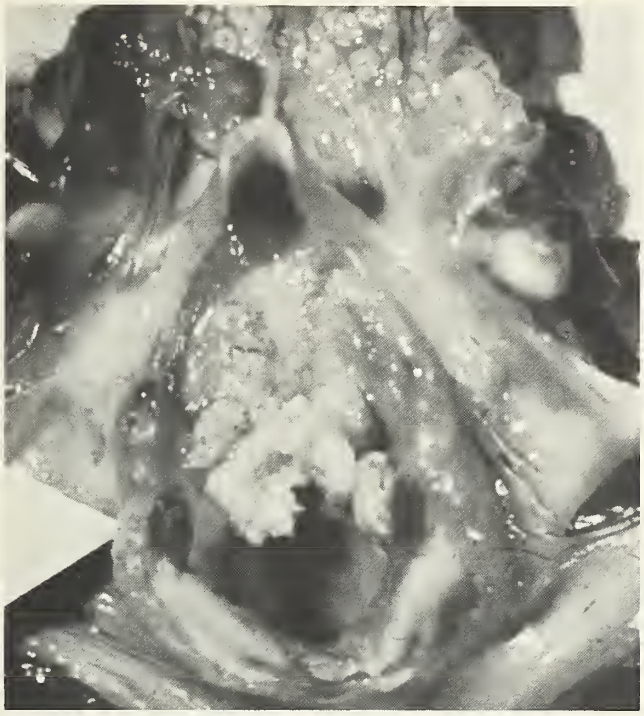


Figure 60
PAPILLOMA
An autopsy specimen from a two year old boy with a history of recurrent vocal cord papillomas since the 6th month of life. Regrowth and neglect caused airway obstruction and death.

trauma, a quality which makes complete removal difficult. Although there was a similar number of cases of juvenile and adult onset laryngeal papillomas in Holinger and associates' 109 cases, 80 percent of juvenile onset papillomas had multiple recurrences, while only 36 percent of adult onset papillomas recurred. Rarely are squamous papillomas reported simultaneously occurring outside the larynx, trachea, or bronchial system.

Recurrence of the laryngeal papillomas, particularly in the juvenile onset group, is a major problem. They can recur literally dozens of times at intervals of one month to a year. The recurrence can extend in the juvenile onset patient well into middle adult life. For no explained reason, they may disappear permanently or recur at any time after the initial removal or recurrence. Recurrences usually occur in the larynx near or at the previous removal site; however, in juvenile onset laryngeal papillomatosis, the recurrence may extend to involve the trachea and bronchi. The recurrent involvement of the trachea and bronchi ended in a fatal outcome in three patients with juvenile onset laryngeal papillomatosis in the AFIP-OTR material. After many years of recurrence, the histologically benign papillomas grew into spaces between the tracheal and bronchial cartilage rings, invading the mediastinum and pulmonary area, with a resulting mediastinitis and death. In an additional six patients with recurring juvenile onset laryngeal papilloma involving the tracheal and bronchial airway, the papilloma extended into the lung parenchyma and after many years led to eventually fatal diffuse infiltration of the lung parenchyma. Malignant change or metastasis in nonirradiated juvenile onset laryngeal papilloma is extremely rare, but has been reported (Bewtra et al.).

In one-third of the patients with adult onset laryngeal papillomatosis in Holinger and associates' series, the histologically benign papilloma showed a recurrence pattern similar to that of the juvenile onset papilloma. Recurrent involvement of the trachea is rare and the fatal complication in the trachea and lung previously mentioned has not been reported in adult onset laryngeal papilloma. Malignant change in adult onset laryngeal papillomatosis is a disputed occurrence and will be discussed below. The recurrence of any laryngeal tumor, particularly in an elderly patient, is cause for alarm to laryngologists, but the recurrent adult onset papillomas should not cause alarm if there is no clinical evidence of aggression and invasion, such as fixation of adjacent laryngeal structures.

Microscopic. The typical laryngeal papilloma of either juvenile or adult onset consists of a thin, vascular, connective tissue core covered by a usually nonkeratinizing, uniform, multilayered, benign squamous epithelium projecting exophytically as primary stalks with additional branching secondary and tertiary stalks (figs. 61-63). The neoplastic squamous epithelium reveals no tendency to invade the stroma or submucosa. Prominent keratin production, either as a surface phenomena or as dyskeratosis, is rarely seen. If present, it suggests the possibility of a

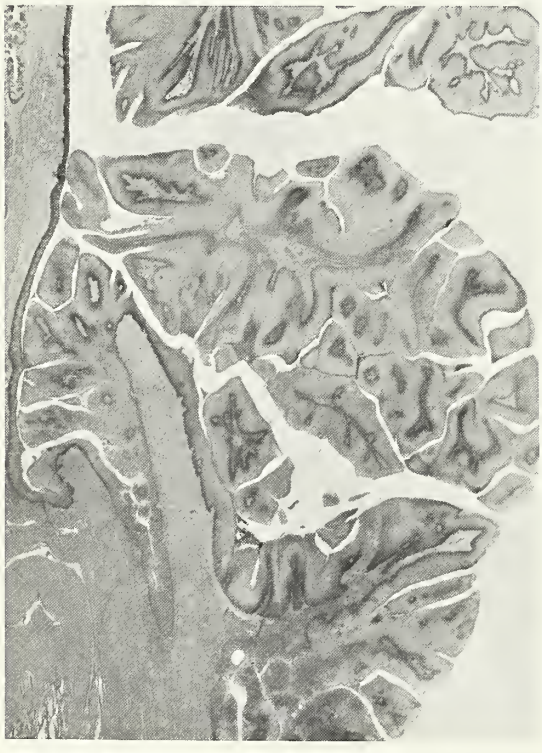


Figure 61
(Figures 61 and 62 are from the same patient)
PAPILLOMA
This is a scanning microscopic view of a juvenile squamous cell papilloma in a 12 year old girl. This represents a recurrence that required laryngectomy because of diffuse involvement. X25.

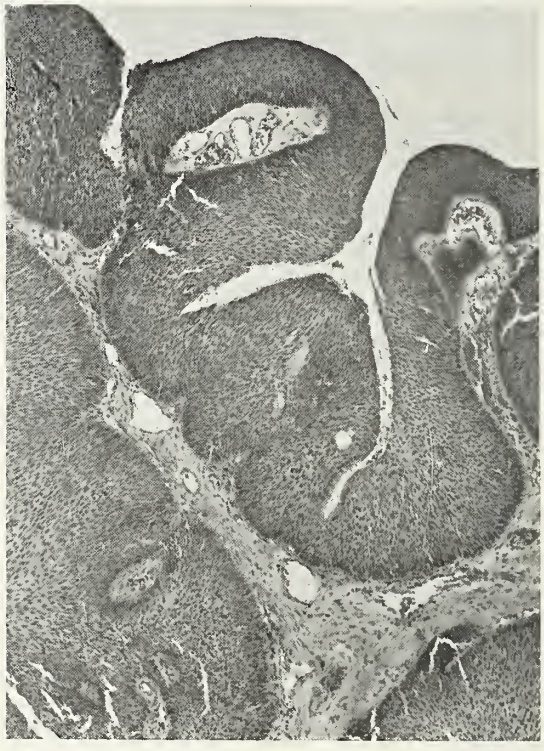
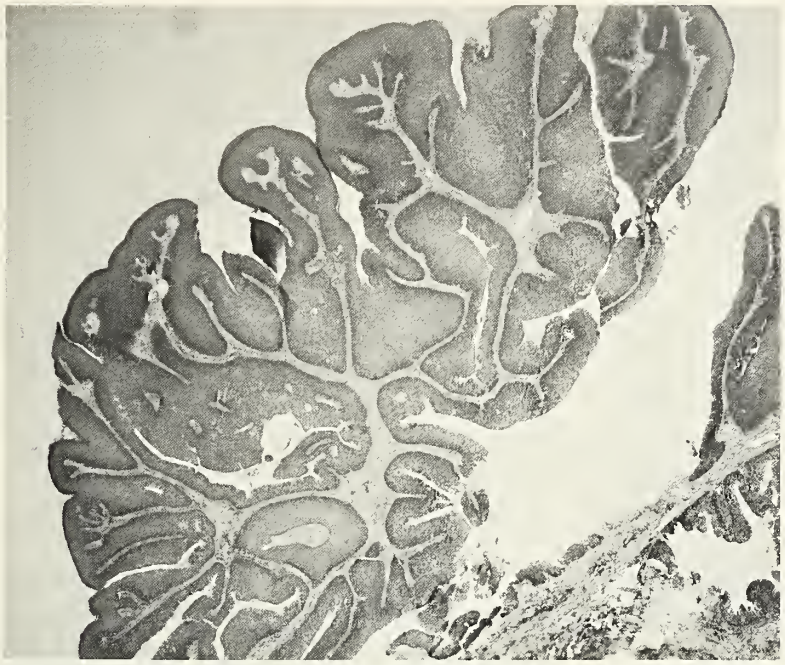
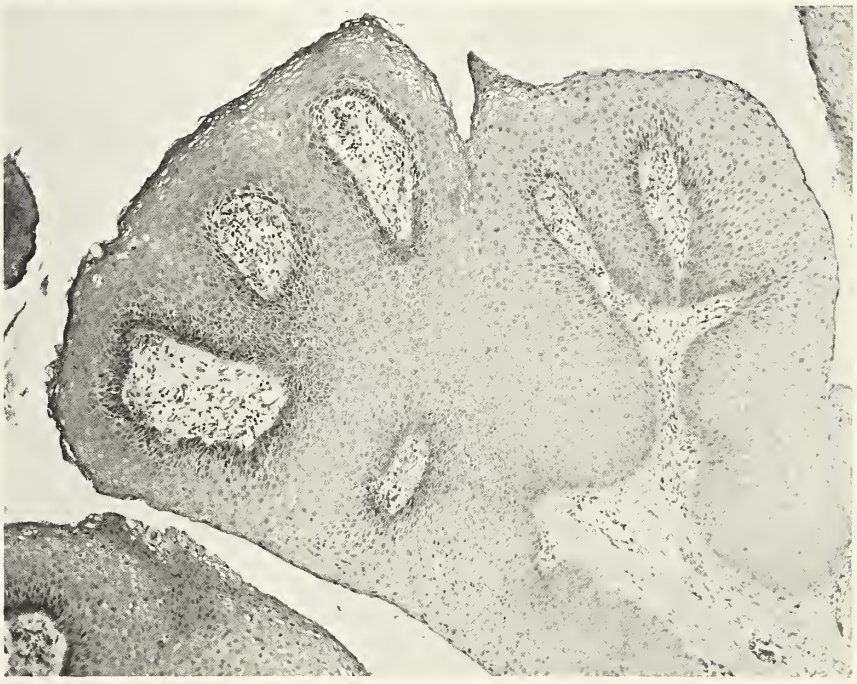


Figure 62
PAPILLOMA
A high power magnification of figure 61 supports a benign, nonkeratinizing, epidermoid neoplastic element. X63.



A



B

Figure 63
PAPILLOMA

(A) This laryngeal papilloma was removed from the true vocal cord of a 62 year old man who had no history of previous laryngeal pathology. X25. (B) Note the uniform, benign, nonkeratinizing, exophytic squamous cell micromorphology. The histology is the same as the juvenile laryngeal papilloma. X160.

verrucous carcinoma. There is little histologic difference seen between the usual benign and adult onset laryngeal papillomas. In the AFIP-OTR material, a certain amount of basal layer epithelial atypia and even mitotic activity has been accepted as a normal occurrence in a benign laryngeal papilloma; however, no particular specific recurrent behavior has been noted accompanying this minimal epithelial atypia, as was reported by Quick and associates (1979).

A previously unreported survey of approximately 200 adult onset laryngeal papillomas contained in the AFIP-OTR material demonstrated a 10 percent incidence of later development of invasive squamous cell carcinoma of the larynx. A reevaluation of the histology of the initial papilloma in cases exhibiting later malignancy revealed a significant epithelial atypia that suggested that the original tumor may have been an exophytic squamous carcinoma. In any patient with an appreciable epithelial atypia, in particular an adult laryngeal papilloma, the area of mucosal attachment of the papilloma should be removed and examined histologically for any evidence of invasion of the underlying stroma (fig. 64).

Differential Diagnosis. The inflammatory and traumatic polyps and nodules of the larynx must be considered in both the pediatric and adult patient in the differential diagnoses, but the microscopic examination should decide the correct diagnosis. In the adult patient, the possibility of an exophytic squamous cell carcinoma must be considered and a course of action is discussed in the previous paragraph. Johnson and associates reported that in 22 patients with adult onset laryngeal papillomas, the majority showed epithelial atypia, but no invasive malignancy developed in follow-up studies lasting 1 to 20 years. They agreed that, because of the experience of others, it would be wise to follow with suspicion any adult with laryngeal papilloma exhibiting cellular atypia.

Treatment. The literature contains numerous technics of laryngeal papilloma removal, such as the CO_2 laser, cryotherapy, ultrasound, or microcauterization, with each supported by enthusiasts, but all methods are essentially a variation of simple surgical removal. No particular technic has decreased the inevitable expected recurrence, although the utilization of the CO_2 laser assures a simple bloodless removal (Strong et al.). Nonsurgical adjuncts, such as estrogen therapy, podophyllin, systemic magnesium, steroids, zinc, Aureomycin, interferon, and the

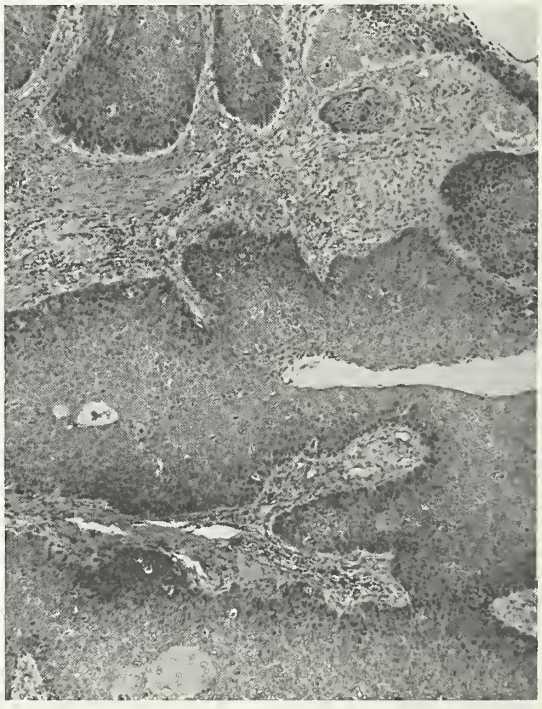


Figure 64
PAPILLOMA
This exophytic laryngeal papillomatous process in a 58 year old man has a diffuse dysplasia of the epidermoid element. This is strongly suspicious of an exophytic squamous cell carcinoma and the possibility of invasion should be ruled out. X160.

use of autogenous vaccine, have all had their advocates, but the overall end results reenforce the fact that all these modalities are only symptomatic treatments. Radiotherapy, however, is to be condemned because of the proven relation of such therapy to malignant carcinomatous transformation, particularly in juvenile onset laryngeal papilloma (Matsuba et al.).

Prognosis. Fatal complications in juvenile onset laryngeal papilloma are below 5 percent in AFIP-OTR material. Airway obstruction and the occasional aggressive invasive behavior described previously are fortunately rare. In the adult laryngeal papilloma, the only serious complication is possible malignant transformation. Such occurrence may be due to the mistaken initial diagnosis of an exophytic squamous carcinoma as a benign squamous papilloma.

Strong and co-workers reported on 76 patients with laryngeal papilloma. Only 28 patients remained free of disease during a follow-up period of one year; only 25 percent of these had juvenile onset papilloma.

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ABNORMALITIES OF SURFACE EPITHELIUM IN THE UPPER RESPIRATORY TRACT

We are assuming the reader is familiar with the histology of both the normal stratified squamous epithelium and the ciliated pseudostratified columnar (respiratory) epithelium that forms the normal surface mucosa of the upper respiratory tract.

Squamous cell metaplasia is not uncommon in areas of the upper respiratory tract normally covered by ciliated pseudostratified columnar epithelium, particularly areas in the trachea, supraglottic larynx, and nasal septum. This multilayered proliferation of histologically benign squamous epithelium replacing the ciliated respiratory mucosa (fig. 65) usually reflects an unnatural physiologic condition, such as abnormal environment and harmful personal habits (smoking), the latter being particularly important in the larynx and tracheal area. Also, physical distortions such as deviated septum or tumor in the nasal area may produce this metaplastic change. Squamous cell metaplasia may also represent the edge of a mucosal malignancy such as squamous carcinoma; therefore, the clinical history and gross appearance of any upper respiratory tract biopsy material revealing histologically only squamous metaplasia is necessary in order to evaluate this possible serious complication.

There is a sequence of cytologic changes that occur in the upper respiratory tract mucosa, particularly those areas consisting of a surface of nonkeratinizing, stratified, squamous epithelium (mainly the true vocal cord). These cytologic changes have been considered premalignant, although the prognostic outlook is usually excellent in properly treated cases. The cause of these mucosal changes is most often traced to the environment or to personal habits of the afflicted patient as a particular reaction to abnormal stimuli.

The least serious is benign squamous cell hyperplasia (acantholysis) (fig. 66). There is no atypia or dysplasia of the proliferating squamous cells, but an increase of basal and/or prickle cell layers may form projections of rete pegs into the underlying stroma

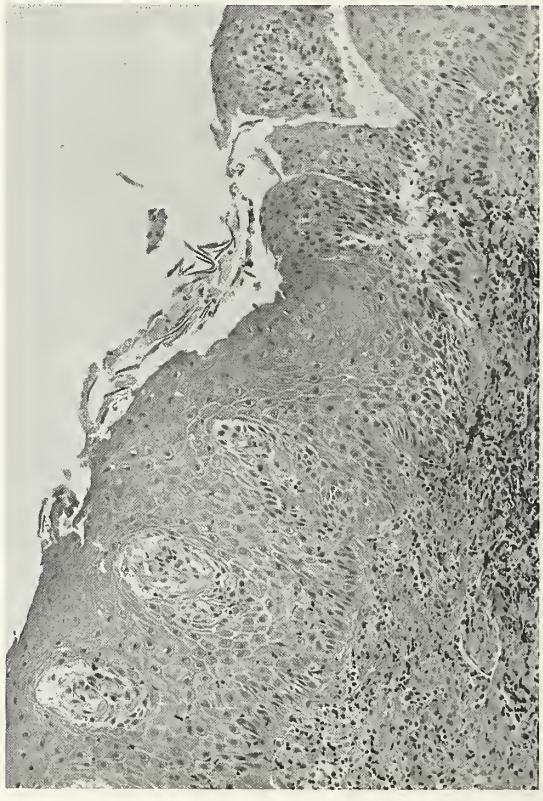

Figure 65
BENIGN SQUAMOUS CELL HYPERPLASIA
A biopsy of the true vocal cord of a middle-aged man revealed, histologically, a benign squamous cell hyperplasia of the mucosa. There is no atypia noted. X160.

and, when pronounced, may be termed pseudoepitheliomatous hyperplasia. The squamous cell hyperplasia may reveal surface keratin that is known histologically as hyperkeratosis or keratosis (fig. 67). An entity involving the larynx, designated as pachyderma laryngis, consists of a diffuse, histologically benign, squamous cell, mucosal hyperplasia involving the major portion of the glottis and possibly portions of the supra- and subglottic mucosa. It occurs most often in older men with a long history of laryngeal abuse.

In the presence of this benign surface hyperkeratosis, intracytoplasmic keratohyaline granules are prominent in the surface prickle cell layer of the epidermis (granulosa cell layer). In the surface keratin layer, the nuclei of cells have disappeared, but if they persist, the pathology is referred to as parakeratosis (fig. 68). Hyperkeratosis (keratosis) and parakeratosis may occur on the surface of a squamous cell carcinoma and the use of the terms hyperkeratosis, keratosis, or parakeratosis as a diagnosis can be quite misleading. These terms are descriptive, macroscopic and at times microscopic adjectives. Dyskeratosis (fig. 69) is interpreted as abnormal keratinization produced in a squamous cell, and may represent a benign or malignant change. The latter situation is often associated with squamous cell carcinoma and,

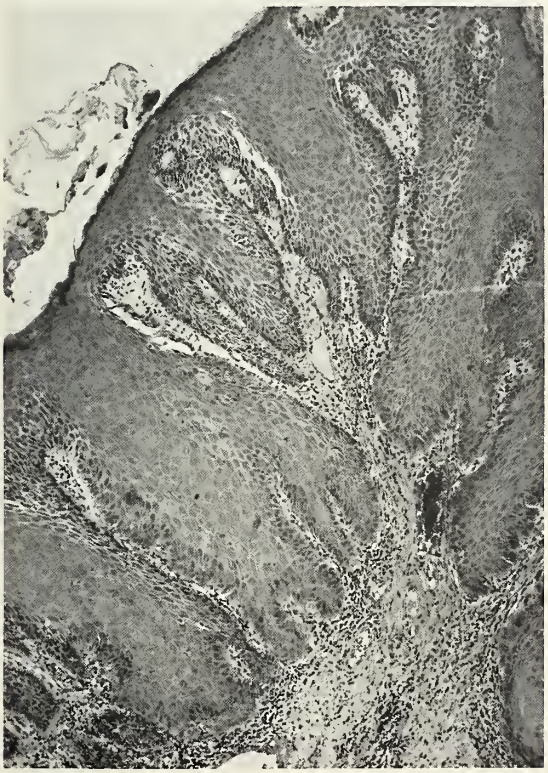

Figure 66
BENIGN SQUAMOUS CELL HYPERPLASIA
A biopsy of the epiglottis revealed extensive hyperplasia and acanthosis, which could qualify as a pseudoepitheliomatous hyperplasia. There is no atypia to the cells. X160.

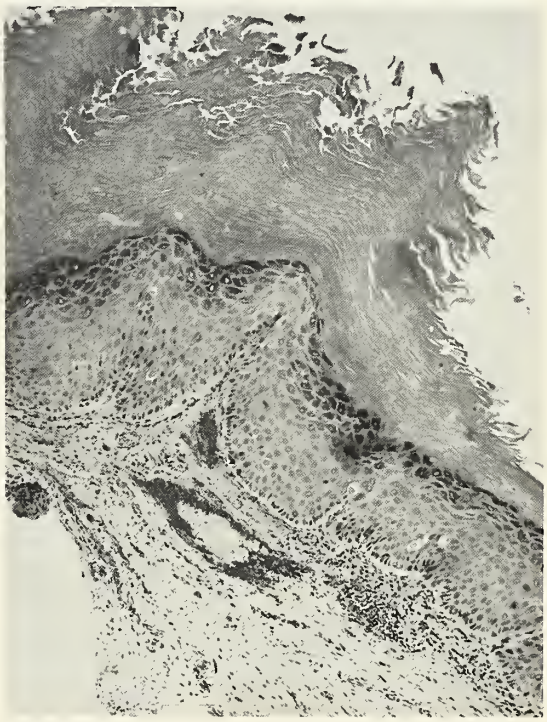

Figure 67
HYPERKERATOSIS
A 68 year old man with chronic hoarseness over many years had several biopsies of suspicious clinical areas of the larynx. All had a histology similar to this of a minimal benign squamous hyperplasia of the mucosa, but with marked hyperkeratosis and a prominent stratum granulosum cell layer. X160.

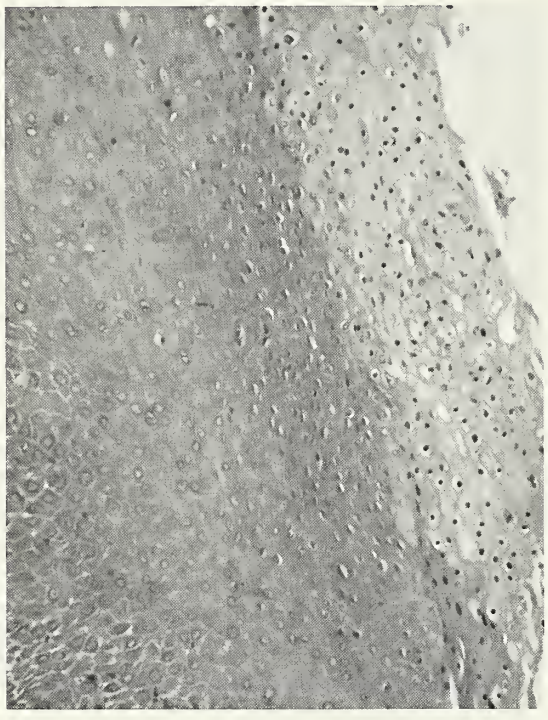

Figure 68
PARAKERATOSIS
This histologically benign, acanthotic squamous cell hyperplasia in a biopsy of the hypopharynx reveals areas of parakeratosis on the mucosal surface, characterized by nucleated keratin material. X160.

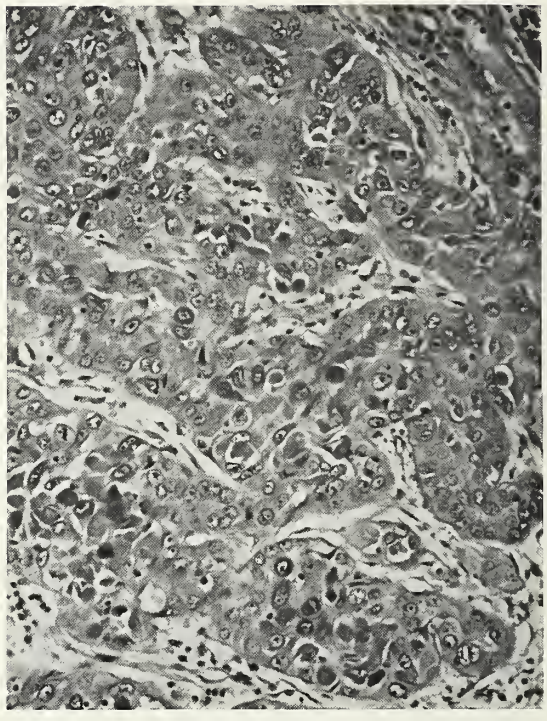

Figure 69
DYSKERATOSIS
A biopsy of well differentiated squamous cell carcinoma of the larynx exhibits prominent dyskeratosis of the squamous tumor cells. Rarely, dyskeratosis may be seen in benign squamous proliferations of the upper respiratory tract mucosa. X160.

therefore, the diagnosis of dyskeratosis alone may be misleading.

The more significant premalignant change is the occurrence of dysplasia (epithelial atypia). The terms dysplasia and epithelial atypia are used here synonymously; however, some feel there are differences between the two (Johnson et al.).

Dysplasia (epithelial atypia) is interpreted in this writing as a process of qualitative alteration in a malignant direction in the appearance of cells. The process usually commences in the deepest aspects of the squamous epithelium, with involved cells revealing nuclear alterations with one or more of the following features: irregularities of the nuclear membrane, often with concentration of chromatin beneath the nuclear membrane to give the rest of the nucleus an empty (Orphan Annie) appearance; an increase in nuclear chromatin content and irregularity in its distribution; and an increase of nuclear size relative to the cytoplasm. The nuclear changes which would be recognized as malignant in cytologic preparations of individual cells are collectively referred to as atypical and dysplastic mucosa (fig. 70). Mitotic activity may also be noted with the above changes.

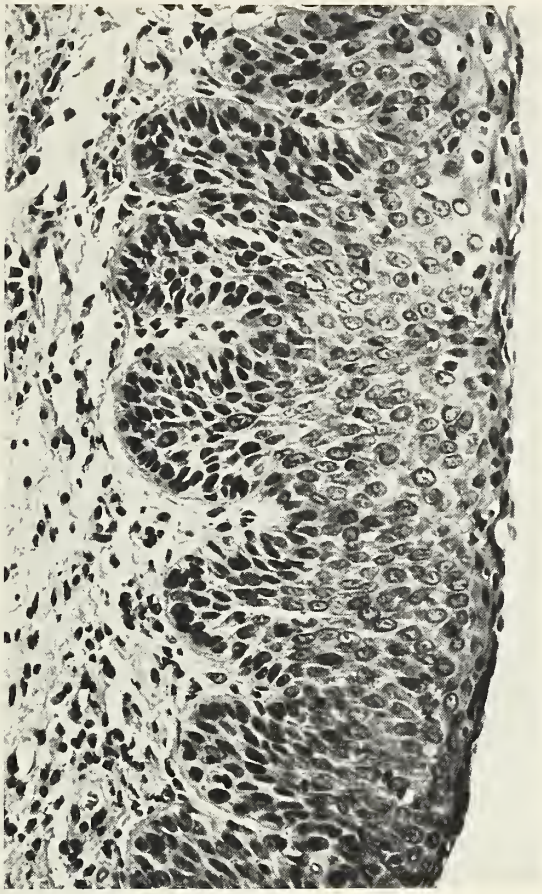

Figure 70
DYSPLASIA
A biopsy of the true vocal cord of the larynx with some hyperplasia of the squamous cell mucosa, but mainly a dysplasia of cells in the basal areas, with an approach to normal maturation toward the surface. X160.

Any degree of dysplastic squamous epithelium short of squamous cell carcinoma (or in situ carcinoma) is most often a potentially reversible process (Friedman; Hellquist et al.; McGavran et al.). Minor degrees of it are found in inflammatory processes after irradiation and in benign squamous papillomas; these do not have the diagnostic connotation of a malignant process.

The pathologic changes of hyperplasia, keratosis, and dysplasia (epithelial atypia) are of significance mainly in the true vocal cord area of the larynx because, even though the pathology may involve adjacent or isolated areas of the upper respiratory tract, in true vocal cord involvement they are usually symptomatic. They disturb the normal contour of the glottis, producing hoarseness. In other anatomic areas of the upper respiratory tract, such premalignant changes cause little disruption and only if they evolve into an aggressive squamous cell carcinoma are they usually symptomatic. Studies of the conditions of hyperplasia, keratosis, and dysplasia involving the true vocal cord of the larynx (McGavran et al.; Norris and Peale; Friedman) and the relationship to later development of squamous cell carcinoma reveal that when vocal cord mucosal changes are diagnosed as hyperplasia or keratosis, only 3 to 4 percent of 65 patients later developed invasive squamous cell carcinoma of the anatomic area. When dysplasia accompanies the keratosis or hyperplasia of the vocal cord mucosa, 8 to 15 percent of 380 patients developed squamous cell carcinoma. The patients, while diagnosed as revealing premalignant changes, were treated conservatively with observation and abstinence from laryngeal irritants. Hellquist and associates correlated the severity of dysplasia of the true vocal cord developing in a series of 193 patients as mild, moderate, and severe, and found squamous carcinoma developing in 2, 12 and 25 percent of the patients, respectively. In these quoted figures, only patients with premalignant changes of the true vocal cord of the larynx are included. In the unpublished experience of the AFIP-OTR material, when isolated keratosis, hyperplasia, and dysplasia originate in supraglottic or subglottic mucosal laryngeal areas, the outlook for development of invasive squamous carcinoma in such anatomic areas appears greater.

SQUAMOUS CELL CARCINOMA IN SITU

SYNONYMS AND RELATED TERMS: Intraepithelial carcinoma; Bowen's disease.

Definition. Squamous cell carcinoma in situ is a pathology of the squamous epithelium in which a cellular dysplasia involves the entire width of the mucosa (or skin), from basement membrane to the outer surface, and is without histologic evidence of invasion beyond the basement membrane (fig. 71). Usually it is necessary to obtain multiple histologic sections of the biopsy material to exclude the presence of concomitant invasive squamous carcinoma.

Site. In the upper respiratory tract, squamous cell carcinoma in situ without concomitant invasive squamous carcinoma is found particularly in the anterior portion of the true vocal cord of the larynx. A diagnosis of squamous cell carcinoma in situ is rarely encountered in other areas of the upper respiratory tract, particularly the nasal cavity or pharynx, but since this neoplastic entity is relatively asymptomatic in these areas, it is probably overlooked until a more aggressive invasive squamous cell carcinoma develops. A diagnosis of squamous cell carcinoma in situ in the supra- and subglottic areas should prompt close observation of the patient for adjacent invasive disease. Bauer and McGavran recorded a high incidence of association of invasive squamous carcinoma and in situ carcinoma of these particular areas.

Incidence. Although findings of large series of laryngeal invasive squamous cell carcinomas indicate that isolated squamous cell carcinoma in situ is an infrequent diagnosis in the upper respiratory tract, an autopsy study by Auerbach and associates revealed an incidence of squamous cell carcinoma in situ in 11.4 percent in the true vocal cord and 4.9 percent in the ventricular fold (false cord) in a general autopsy population.

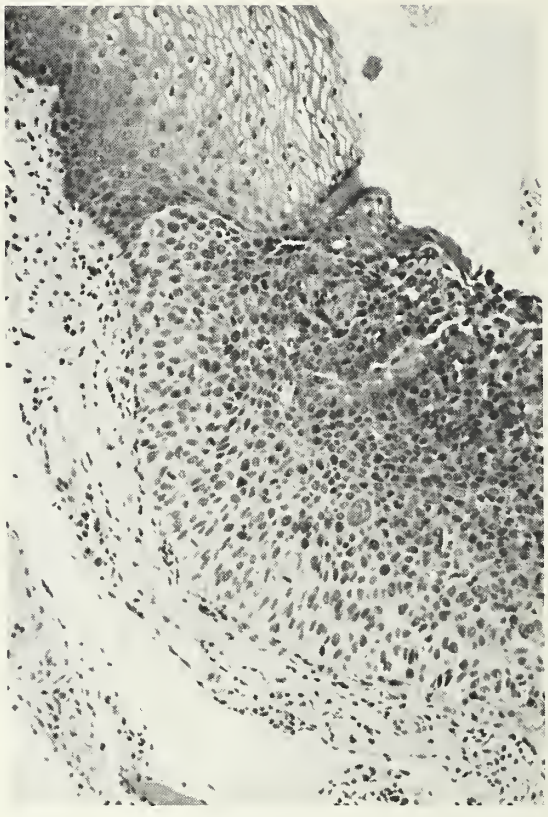

Figure 71
SQUAMOUS CELL CARCINOMA IN SITU
This represents an area of clinical suspicion on the true vocal cord of a 48 year old man. The histology supports a squamous cell carcinoma in situ characterized by dysplastic cells extending from the basement membrane to the surface without evidence of invasion. X160.

Gross. When carcinoma in situ without invasion involves the true vocal cord, the area may appear circumscribed or diffuse, with a gray, white, or red, smooth to granular appearance.

Microscopic. The dysplastic process involves the entire thickness of the squamous epithelium with a loss of cell stratification (fig. 71). The surface cells are often flattened, and the presence of surface keratosis should

suggest the possibility of papillary or polypoid keratinizing carcinoma. Multiple sections should be processed to rule out invasion. The squamous carcinoma in situ transformation often involves the ducts and acinous structures of adjacent mucoserous glands, particularly in the region of the anterior commissure of the true vocal cord.

Treatment. Squamous cell carcinoma in situ is diagnosed mainly in the larynx, particularly in the true vocal cord, and therapeutic modalities range from radiation, mucosal stripping, and local surgical removal (laryngofissure). Miller is of the opinion that the laryngofissure operation offers least treatment failure, while radiation offers the most. Hintz and associates support the more conservative radiotherapy, plus a diligent watchful observation of the patient, as offering as good a prognosis as surgical therapy.

Relation to Invasive Carcinoma. Knowledge of the natural history of carcinoma in situ of the larynx is not as detailed as with the same lesion found in the uterine cervix. There probably is a latent period in which the condition remains in situ, at the end of which the carcinoma will begin to invade. On a detailed histologic reexamination, a large proportion of diagnosed cases of squamous cell carcinoma in situ of the larynx will reveal concomitant invasive carcinoma (Bauer and McGavran).

SQUAMOUS CELL CARCINOMA OF THE NASAL VESTIBULE

This anatomic area (the nasal vestibule) in the anterior nasal cavity is essentially an extension of the external nose and facial skin. The normal histology consists of a keratinizing squamous cell epidermis, a dermis and subcutaneous tissue containing the usual skin adnexa, the latter particularly prominent in the anterior portion of the vestibule. The most common malignant neoplasm of the anatomic area is the squamous cell carcinoma (Goepfert et al.), usually of a well differentiated histology (fig. 72). The patient is most often an older male (male to female ratio is 4 to 1 according to Kagan and associates), with the anterior septum and columella the common area of involvement. Goepfert and associates record one-third of their patients developing submental or preauricular cervical lymph node metastasis. Kagan and colleagues reported that one-third of

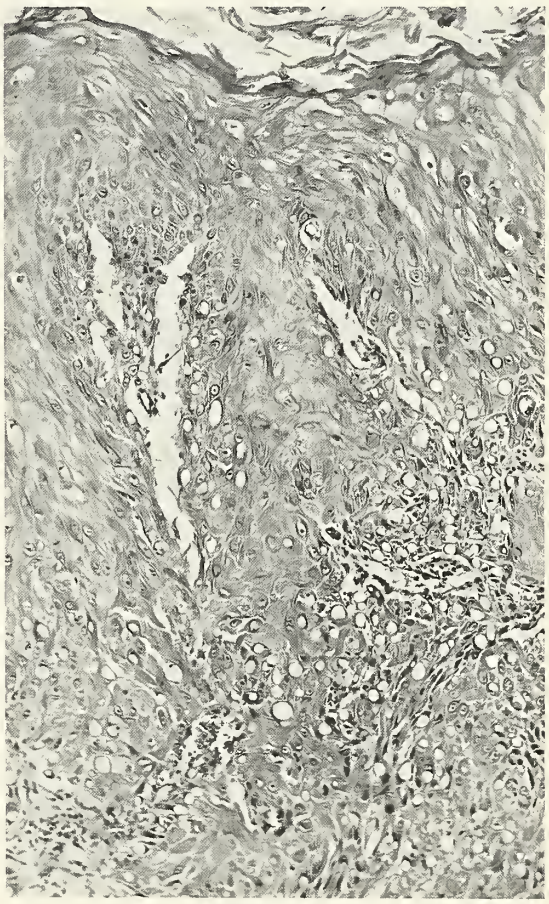

Figure 72
SQUAMOUS CELL CARCINOMA
This is the histology of a well differentiated squamous cell carcinoma of the nasal alar. X160.

their 42 patients died of the neoplasm. They felt that early carcinomas of the vestibule and those that had no bone destruction or lymph node metastases did well regardless of the choice of irradiation or surgical treatment. Late or extensive lesions did poorly regardless of therapeutic modality, including combination therapy.

SQUAMOUS CELL CARCINOMA OF THE MUCOSA OF THE UPPER RESPIRATORY TRACT (RESPIRATORY EPITHELIAL CARCINOMA)

The great majority of malignant epithelial neoplasms arising from the mucosa of the upper respiratory tract (sinonasal tract, pharynx, larynx, and trachea) represent a form of squamous cell carcinoma (epidermoid carcinoma), either of the keratinizing or nonkeratinizing type. The latter has been referred to as a transitional carcinoma or lymphoepithelioma. Verrucous carcinoma and spindle cell carcinoma (squamous cell carcinoma with sarcomatoid stroma) are included in a specialized group of squamous cell carcinomas that quite often has its origin in the upper respiratory tract. There is also support for adenocarcinoma and melanoma as arising from the upper respiratory mucosa, and these particular neoplasms will be discussed in a later section of this Fascicle.

SQUAMOUS CELL CARCINOMA OF THE SINONASAL TRACT MUCOSA

SYNONYMS AND RELATED TERMS: Transitional carcinoma; cylindrical (cell) carcinoma; nonkeratinizing carcinoma; Ringertz carcinoma.

Frequency and Age. Of the 2800 cases of neoplasia of the sinonasal tract (representing 16 percent of all upper respiratory neoplasia) accessioned by AFIP-OTR between 1939 and 1976, there were 312 patients with paranasal sinus cavity respiratory mucosal carcinoma and 202 patients with primary nasal cavity respiratory mucosal carcinoma. The maxillary sinus origin accounts for 80 percent of all paranasal sinus respiratory mucosal carcinoma. The lateral nasal wall and floor gave rise to 85 percent of the nasal cavity mucosal carcinoma. Pediatric patients (birth to 16 years) accounted for 12 cases of nasal cavity mucosal carcinoma and 12 cases of paranasal sinus mucosal carcinoma. The youngest patient was two years of age at diagnosis; however, the majority of pediatric patients were over seven years of age at diagnosis. Muir and Nectoux found the highest age-specific incidence rate occurring between the ages of 65 and 80 years in males, whereas females experienced an increase beyond the age of 80 years. The ratio of male to female was 2 to 1.

Histogenesis. There is a suggested increase in respiratory mucosal carcinoma in boot and shoe industry workers, and a 40 to 1 ratio of observed to expected cases of sinonasal mucosal squamous cell carcinoma in nickel workers (Muir and Nectoux). An increased risk of nasal cavity carcinoma is suggested in chromate workers, workers exposed to flour dust, and textile workers, but further investigation in these industries is needed. Ethmoid sinus carcinoma in isopropyl alcohol manufacture is reported. Muir and Nectoux mentioned that clinicians in Japan observed that 80 percent of cancers of maxillary sinus were linked to previous long-standing chronic sinusitis; however, the AFIP-OTR clinical information does not support such a connection. Preston-Martin and associates feel that tobacco and alcohol users are apparently at no unusual risk in sinonasal carcinoma, but Beatty and col-

leagues feel smoking has an etiologic role in at least septal and nasal vestibule carcinoma.

Clinical. Primary respiratory mucosal carcinomas of the nasal cavity are usually recognized comparatively early in their evolution because such symptoms as airway obstruction, epistaxis, and nasal drainage prompt early clinical investigation, with biopsy material providing the diagnosis. Beatty and associates, in 61 patients of nasal septum primary mucosal carcinoma, supported approximately two-thirds of the cases presenting in the anterior nasal septal area, where signs and symptoms presented early. Such is not the case with paranasal sinus mucosal carcinoma, because common early sinus symptoms such as cheek pain and swelling, oral-dental and eye complaints, and persistent headaches will more often be attributed to inflammatory paranasal sinus disease and so treated. It is not until such advanced symptoms as facial deformity, proptosis, nasal cavity mass, rhinorrhea, or trismus that the true nature of the disease is recognized. Paranasal sinus exploration and biopsy on every patient complaining of sinus signs and symptoms is not practical. Unfortunately, usually six months to a year evolve after initial symptoms before the correct diagnosis of carcinoma of the paranasal sinus is made. Any patient with unusually severe paranasal sinus symptoms, particularly severe unrelieved pain, deserves diagnostic exploration.

The prognosis of sinonasal mucosal carcinoma is linked to clinical staging according to the TNM method of the American Joint Committee for Cancer Staging and End Results reporting; however, the staging classification applies only to maxillary sinus cancer. One could probably adopt this staging system to the remaining paranasal sinuses or nasal cavity anatomy. The T1 stage is the rarest encountered and is designated when the neoplasm is confined to the mucosa of the infrastructure, with no bone erosion or destruction. The T2 stage designates early bone destruction, but in a less complicated area of the maxillary sinus, such as the medial and anterior wall. Most of the patients with maxillary sinus respiratory mucosa carcinoma, when initially diagnosed, fall into the T3 stage, where a more extensive neoplasm invades the skin of the cheek, orbit, anterior ethmoid sinuses, or pterygoid muscle. The T4 stage is when massive neoplasm invades the cribriform plate, posterior ethmoids, sphenoid, nasopharynx, pterygoid plates, or base of the skull. Batsakis and associates quote an incidence of regional lymph node metastases in sinonasal cancer from 10 to 22 percent at original presentation or diagnosis, with an additional 8 to 16 percent revealing regional lymph node metastasis at a later date. Robin and Powell, in 624 cases of sinonasal tract malignancies, found regional nodes involved in 14.3 percent, with disseminated metastasis in 1.6 percent.

Radiologic evaluation has revealed opacification and bone erosion in 80 percent of patients with maxillary sinus carcinoma (Tabb and Barranco). The percentage of x-ray designated destruction of primary nasal cavity respiratory mucosal carcinoma is lower, probably because of the expected earlier diagnosis.

Gross. Because of the difficulty of adequately viewing the in vivo respiratory mucosal carcinomas in the limited anatomic confines of the sinonasal tract, a distinctive, recognizable gross presentation is not described. In the AFIP-OTR material, except for the few cases suggesting a papillomatous growth, the majority of the respiratory mucosal carcinomas were recognized as malignant-appearing tumors with a gray to

pink or red, friable, fungating growth, quite susceptible to bleeding or manipulation. The invasion into surrounding bony walls and adjacent vital cavities add to the malignant appearance.

Microscopic. Approximately 80 to 85 percent of the sinonasal tract respiratory mucosal carcinomas are recognized at least in part as keratinized squamous carcinoma (fig. 73). This supports the concept of the ability of the basal cell layer of the normal pseudostratified, columnar, ciliated, respiratory epithelium to differentiate into a malignant keratinized squamous epithelium or to form benign squamous neoplasms, such as sinonasal tract papillomas. The overall structure of the keratinizing squamous cell carcinoma of the sinonasal tract mucosa tends to be poorly differentiated. Papillary exophytic or so-called inverted architectural epithelial formations are not unusual in the poorly differentiated respiratory sinonasal tract squamous cell carcinoma and pathologists may pass over these particular neoplastic patterns, designating them as benign papillomas, if they neglect to pay attention to the micromorphologic details. The purely transitional, cylindrical, columnar Ringertz or well differentiated, nonkeratinizing, squamous cell carcinomas comprise the remaining 15 to 20 percent of sinonasal respiratory mucosal carcinomas. These groups are cytologically carcinomas with elongated cells, oriented perpendicular to the carcinoma surface, an intact basement membrane, and a lack of surface keratinization (figs. 74, 75). Desmosomes are difficult to demonstrate by light microscopy, but ultrastructure study will usually demonstrate the characteristics of squamous epithelium (desmosomes, tonofibrils, keratohyalin granules). Keratinizing or nonkeratinizing respiratory mucosal carcinoma of the sinonasal tract may produce

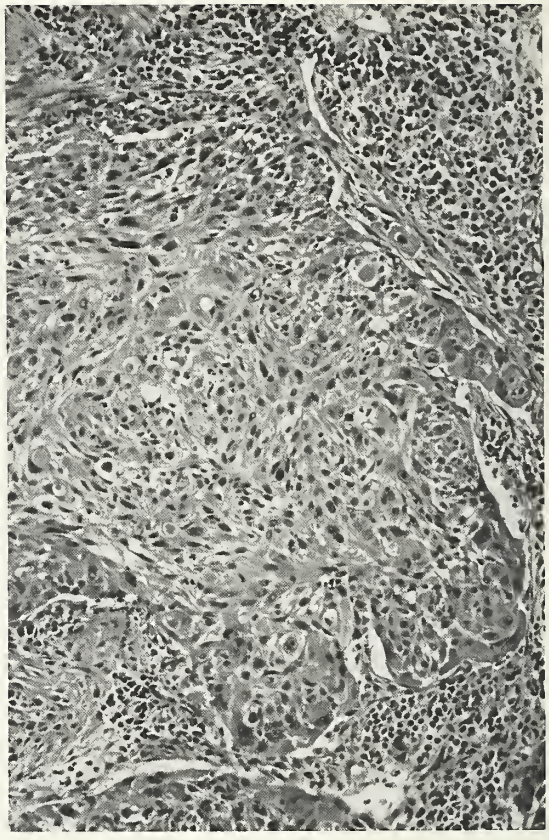

Figure 73
SQUAMOUS CELL CARCINOMA
A high magnification reveals dyskeratosis and suggestive desmosomes in focal areas, as well as a poorly differentiated squamous cell carcinoma morphology. X160.

mucus located either intra- or intercellularly. This finding is more likely due to the retention of the mucus-producing cell (goblet cell) of the basal cell layer of the respiratory mucosa. The terminology of adenosquamous carcinoma and mucoepidermoid carcinoma has been utilized in this mucus containing squamous cell carcinoma of the upper respiratory tract; however, the presentation, treatment, and prognosis is that of a squamous cell carcinoma.

Treatment and Prognosis. Therapy has been a point of conjecture in respiratory mucosal carcinoma of the sinonasal tract and

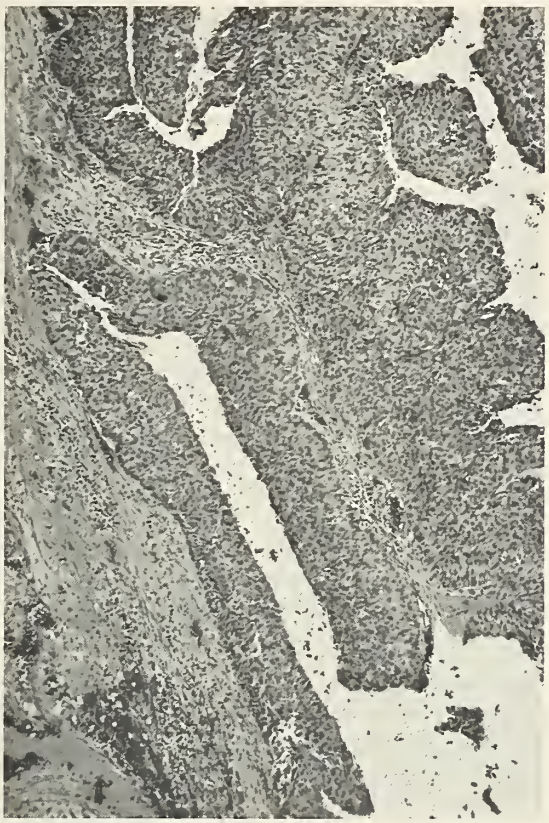

Figure 74
(Figures 74 and 75 are from the same patient)
SQUAMOUS CELL CARCINOMA
This papillary-like mucosal carcinoma of the maxillary sinus is also considered a transitional or cylindrical cell carcinoma. X63.

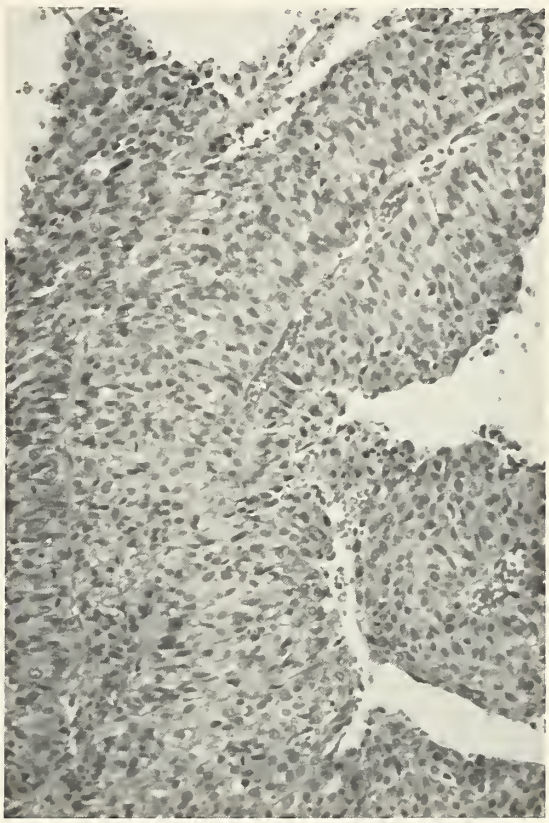

Figure 75
SQUAMOUS CELL CARCINOMA
Note the tall, elongated, columnar type neoplastic cells perpendicular to the basement membrane, with a fair degree of uniformity, but no obvious keratin. X160.

probably will vary according to whether the therapist is a surgeon or a radiotherapist. Lee and Ogura felt that maxillary sinus carcinoma treated with combined full-dose preoperative radiation, followed by radical surgical removal, yielded over a 38 percent five-year tumor-free survival. Those cases with lower clinical staging were the greater benefactor (stage T1, a 60 percent five-year survival; stage T2, a 45 percent five-year tumor-free survival). Ellingwood and Million stated that with radiation therapy alone they obtained a 54 percent five-year tumor-free survival in 13 patients with ethmoid/sphenoid sinus cancer. Bosch and colleagues obtained an overall 56 percent, five-year tumor-free survival in 40 patients with nasal cavity cancer, utilizing radiation therapy. Weimert and associates identified 97 patients with nasal septal carcinoma in the medical literature up to 1977, including 14 patients of their own, 2 of whom died of the disease. Irradiation, surgical removal, and combined therapy had been employed, but Weimert and colleagues felt that prognosis did not correlate with histologic grade of the neoplasm, but was inversely related to the size of the carcinoma at the time of diagnosis and the presence of

metastasis. Beatty and associates, in a report on 85 patients with nasal septal carcinoma, found that one-third developed local or distant metastases and felt that an 89 percent five-year, and a 76 percent 10-year survival could be expected in adequately treated cases.

SQUAMOUS CELL CARCINOMA OF THE NASOPHARYNX MUCOSA

SYNONYMS AND RELATED TERMS: Lymphoepithelial carcinoma; lymphoepithelioma (Regaud or Schmincke type); transitional carcinoma; carcinoma of the respiratory membrane (well and poorly differentiated, keratinizing and nonkeratinizing); embryonal carcinoma; scirrhous carcinoma; undifferentiated carcinoma; nonkeratinizing carcinoma; nasopharyngeal carcinoma (NPC).

The nasopharynx is that part of the airway extending from the sphenoid bone superiorly, from the posterior surface of the choana and palate anteriorly, and is bordered posteriorly by the basilar process of the occipital bone and the cervical vertebrae. Its uniqueness lies in its anatomy, the nonkeratinizing carcinoma that comprises the majority of the nasopharyngeal malignant neoplasms, and the epidemiology and immunology that surround this group of nasopharyngeal carcinomas.

Frequency and Age. There were 2025 cases of nasopharyngeal neoplasia recorded in the AFIP-OTR from 1939 to 1976, representing 9 percent of all upper respiratory neoplasia. Seventy-five percent of all recorded nasopharyngeal neoplasms were classified as squamous cell carcinomas of mucosal origin. The incidence per 100,000 population ranges from .6 for males and .1 for females in the United States, to 20 males and 10 females in the Kwantung Province in the Peoples Republic of China (Batsakis et al.). The male to female ratio is 5 to 1 among whites, and 4 to 1 among blacks in the United States. All age decades were susceptible, with a gradual increase in whites from pediatric age to the seventh decade, when a sharp drop occurs, while in blacks the highest incidence is in the first two decades of life (Easton et al.). Shanmugaratnam and associates, in Singapore, recorded a gradual increasing incidence in the first three decades, with a sharp increase in the fourth, fifth, and sixth decades, then a decline in the seventh and older groups. They also noted that the younger the patient, the more undifferentiated was the histology of the nasopharyngeal mucosal carcinoma; the older patients tended toward a more differentiated squamous cell mucosal carcinoma.

Etiology and Epidemiology. Probably no investigation of possible etiologic factors has been more intense than that of the nasopharyngeal carcinoma. Environmental factors, such as smoking, poor ventilation, and use of herbal drugs and nasal balms, represent some implicated but as yet unproven causes. The possible role of ingested carcinogens (dimethylnitrosamine) in salted fish, a traditional food in southern China, has received particular attention. The viral implication has also received much attention and investigation. IgG, IgM, and IgA components of antibodies to the Epstein-Barr virus capsid and early antigens, as well as a high frequency of Epstein-Barr viral-associated serum IgA, have been found in patients with nasopharyngeal mucosal carcinoma, all of which have been regarded as useful for monitoring the course of the disease, effects of treatment, and evaluating prognosis. These studies have not led to a definite determination as to whether the virus is merely a passenger or is etiologically responsible. Genetic studies have revealed that distinctive histocompatibility antigen (HLA) patterns play a definite role in nasopharyngeal mucosal carcinoma. That susceptibility and survival can

be correlated with the host's HLA type has been clearly defined in Chinese patients. Age is essentially unimodal in nasopharyngeal carcinoma in high risk areas, such as China, Hong Kong, and Singapore, with children being less than 1 percent of the total affected population. In the United States, Greece, and Tunisia, around 20 percent of the population affected by nasopharyngeal carcinoma were younger than 30 years. Black children in the southern United States have a four- to sevenfold increased risk of nasopharyngeal carcinoma, as compared with their caucasian peers (Batsakis et al.).

Gross. Because of the limited anatomic area of the nasopharynx, the pathologist will usually receive only a small biopsy specimen with no characteristic gross descriptive qualities.

Microscopic. The pathologic classification is most controversial and confusing. Many classifications are presented in the literature, but for consistency's sake, the classification proposed by the World Health Organization (WHO) is recommended. One has only to remember that all mucosal carcinomas of the nasopharynx are squamous cell carcinoma and that the only variable is the degree of differentiation (Michaels and Hyams). The WHO classification lists three categories: (A) Squamous cell carcinoma (keratinizing squamous cell carcinoma) which reveals intercellular bridges and/or keratinization over most of its extent. It may be graded as well, moderately, or poorly differentiated. (B) Nonkeratinizing carcinoma which has evidence of differentiation with a maturation sequence that results in cells in which squamous differentiation is not evident on light microscopy. The tumor cells have fairly well defined cell margins and show a stratified or pavement, but not syncytial epithelium (figs. 76, 77). (C) Undifferentiated carcinoma (of nasopharyngeal type), with tumor cells that have oval or round vesicular nuclei, prominent nucleoli, indistinct cell margins, and a syncytial rather than pavement appearance (figs. 78, 79). Spindle-shaped cells, some with hyperchromatic nuclei, may be present. There may be irregular and moderately well defined masses and/or loosely connected cell strands in a fibrous scarlike or lymphoid stroma. Mucin production may be seen in the more well differentiated keratinizing squamous cell carcinoma or nonkeratinizing carcinoma.

The terminology lymphoepithelioma is not encouraged because of the varied interpretations by its users, such as possibly representing peculiar type of lymphoma. Nasopharyngeal mucosal carcinoma with a prominent lymphocytic accompaniment would be referred to as undifferentiated (or rarely keratinizing squamous carcinoma or nonkeratinizing carcinoma) with lymphoid stroma. The Schmincke or Regaud classification of the so-called lymphoepithelioma has no logical application in nasopharyngeal mucosal carcinoma.

Michaels and Hyams, in an ultrastructural examination of nasopharyngeal mucosal undifferentiated carcinoma (fig. 80), indicated desmosomes and poorly defined tonofilaments were detectable and varied in prominence directly to the degree of differentiation of the neoplasm as determined under the light microscope.

In the United States, Easton and associates, in 177 patients with nasopharyngeal mucosal carcinoma, found 82 percent as being undifferentiated carcinomas, 14 percent keratinizing squamous cell carcinomas, and 4 percent nonkeratinizing carcinomas, while Shanmugaratnam and associates, in Singapore, histologically classified 363 patients as 47 percent having undifferentiated

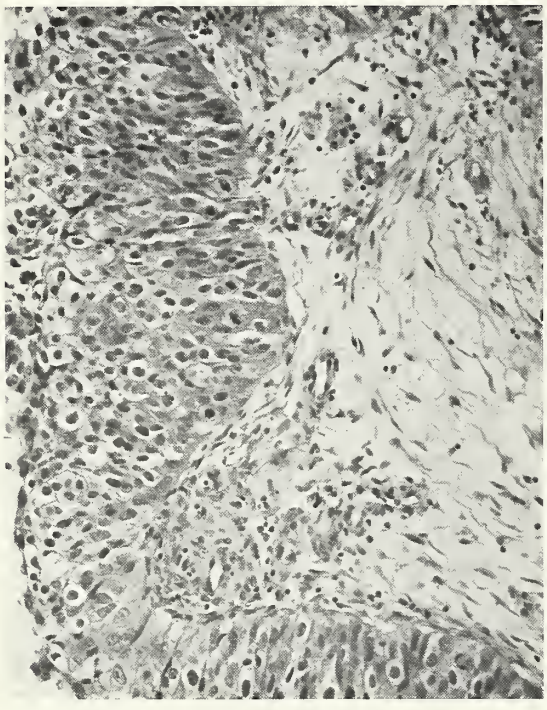

Figure 76
SQUAMOUS CELL CARCINOMA
This is nonkeratinizing carcinoma of the nasopharynx (World Health Organization [WHO] classification). The micromorphology is essentially that of the cylindrical or transitional cell type in a sinonasal tract squamous cell carcinoma. X200.

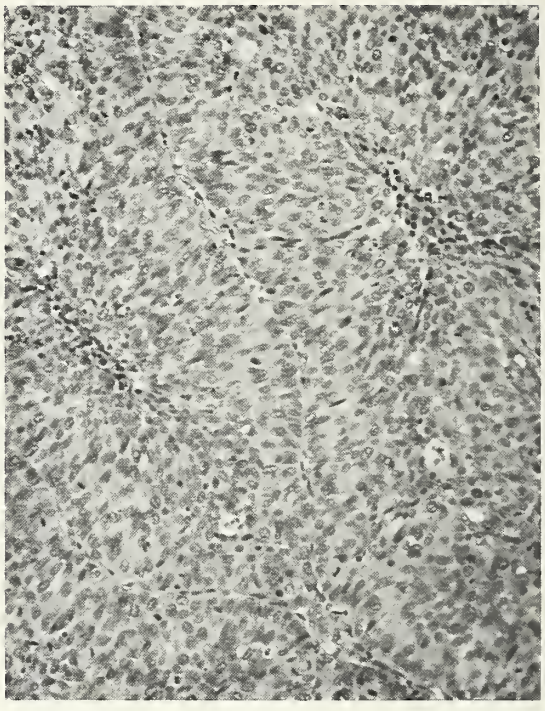

Figure 77
SQUAMOUS CELL CARCINOMA
Another example of the so-called nonkeratinizing carcinoma of the nasopharynx (WHO classification). X160.

carcinoma, 20 percent keratinizing squamous cell carcinoma, and 33 percent nonkeratinizing carcinoma.

Differential Diagnosis. That non-Hodgkin's lymphomas of this area pose the most frequent diagnostic differential problem is shown by consultative material received at the AFIP. Understandably, the undifferentiated nasopharyngeal carcinoma and undifferentiated non-Hodgkin's lymphomas may have a similar structure, but if light microscopic examination is not conclusive for a definite diagnosis, certain other helpful diagnostic examinations, such as electron microscopic examination, immunoperoxidase technics, and the Epstein-Barr viral antibody studies should help solve the particularly difficult case.

Clinical. In 49 percent of Baker's 120 patients with nasopharyngeal malignancies, there was hearing loss due to eustachian tube involvement together with an accompanying otitis media. In 47 percent of his patients, the initial symptom was the presentation of a neck mass. Other symptoms in his series, in decreasing order of frequency were nasal obstruction, epistaxis, pain, and headache. Cranial nerve dysfunction was present in 17.5 percent of the 120 patients, the fifth cranial nerve most often involved, and only the olfactory and optic nerves were completely spared.

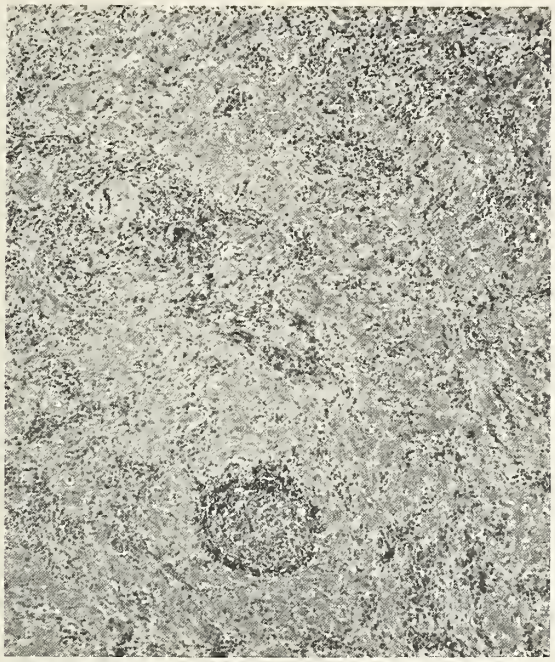

Figure 78
(Figures 78 and 79 are from the same patient)
SQUAMOUS CELL CARCINOMA
In this undifferentiated carcinoma of the nasopharyngeal type (WHO classification), there is prominent, histologically benign, lymphoid tissue infiltrate which has led to these neoplasms being referred to as lymphoepitheliomas, a rather confusing designation. X63.

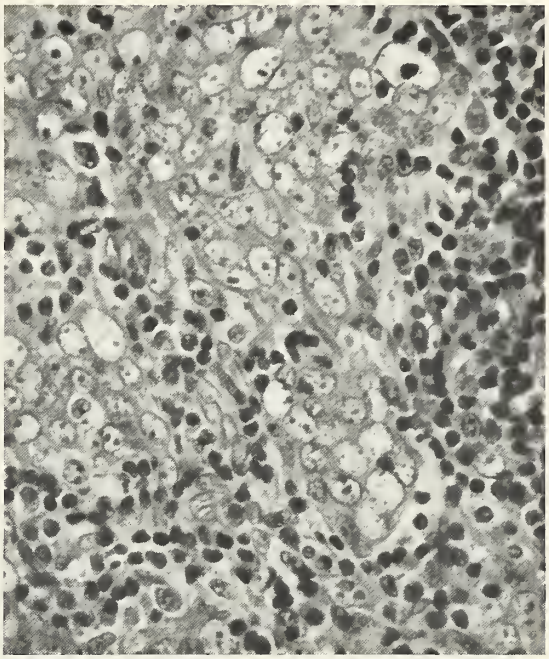

Figure 79
SQUAMOUS CELL CARCINOMA
A higher magnification reveals the oval and rounded vesicular nuclei, prominent nucleoli, indistinct cell margins, and a syncytial rather than pavemented appearance characteristic of the undifferentiated carcinoma of the nasopharynx. X400.

Often the primary nasopharyngeal carcinoma will be quite minute, thus occult, and the diagnosis is unobtainable until a neck mass appears, with metastatic nasopharyngeal carcinoma to a lymph node. Random biopsies (never "blind" biopsies) of a clinically normal nasopharynx may be unrewarding and perhaps a curettage adenoidectomy type biopsy might be more productive. When a nasopharyngeal mass is clinically detected in nasopharyngeal carcinoma, the lateral walls, including the fossa of Rosenmuller, are the most common sites of origin, followed by the posterior superior wall, with less than 10 percent arising from the anterior wall (Batsakis et al.).

According to the American Joint Committee for Cancer Staging, the clinical staging of nasopharyngeal malignancies is: T1 as tumor confined to one site of the nasopharynx or no tumor visible (positive biopsy only); T2 as tumor involving two sites (both posterior and lateral walls); T3 as extension into the nasal cavity or oropharynx; and T4 as tumor invasion of skull or cranial nerve involvement, or both.

Treatment and Prognosis. The complex anatomy of the nasopharynx has made the treatment of mucosal carcinoma of this region the realm of the radiotherapist, with little contribution by the chemotherapist or surgeon at this time. Hoppe and associates,

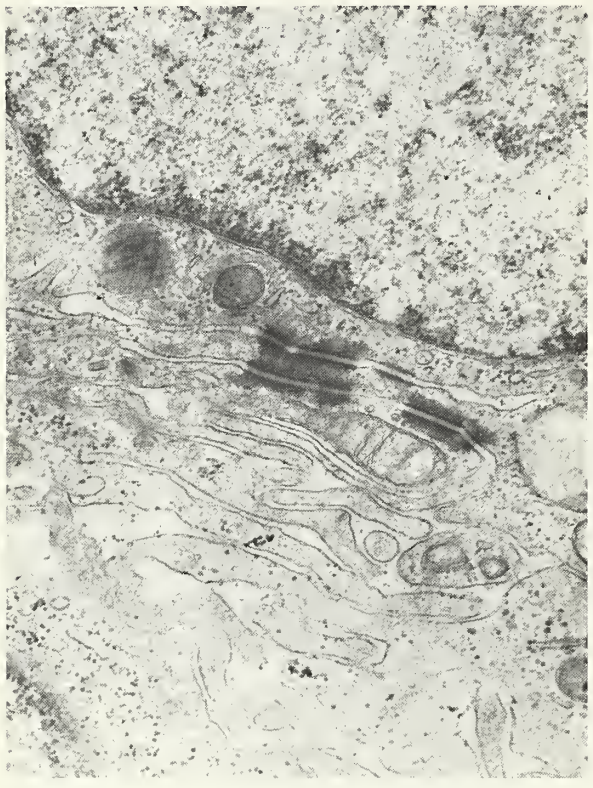

Figure 80
SQUAMOUS CELL CARCINOMA
An electron micrograph of an undifferentiated carcinoma of the nasopharynx reveals prominent desmosomal structures in areas of contact cytoplasmic processes. Although not visible in this view, tonofibrils are usually quite apparent. The findings are those of squamous cell carcinoma. X20,000.

utilizing radiotherapy, obtained 76, 58, and 55 percent five-year survivors with no evidence of residual neoplasm, respectively, in T1, T2, and T3 lesions. These patients were without proven regional lymph node metastasis on diagnosis. Patients with cervical lymph node metastasis had a 10 to 20 percent less favorable survival.

Huang and Chu, Chang and associates, and Mesic and associates, with large numbers of patients, revealed a slightly less favorable outcome following radiation therapy. Shanmugaratnam and associates found that following radiotherapy, patients with keratinizing squamous cell carcinomas had the poorest five-year survival (11 percent), while patients with nonkeratinizing and undifferentiated carcinomas had a 27.6 and 30.1 percent five-year survival following radiation. The amount of lymphocytic infiltration accompanying the carcinoma affected the three-year survival when markedly increased to 45.8 percent, but the five-year survival (36.5 percent) was comparable to groups with less significant or no lymphocytic infiltration. The patients of Shanmugaratnam and associates revealed significant responsive difference according to age. Under 30 years of age they did well, with a 53.3 percent five-year survival; 30 to 49 years of age, a 27 percent five-year survival; and over 50 years of age, a 16.6 percent five-year survival. Also, in his studies, female patients had a 42.9 percent five-year survival and males a 19.5 percent five-year survival.

MUCOSAL SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX AND HYPOPHARYNX

The oropharynx is that part of the pharynx that extends from the plane of the hard palate to the level of the hyoid bone inferiorly and is contiguous with the oral cavity. The lower pharynx is the hypopharynx, which extends from the lower border of the oropharynx (hyoid bone) to the lower border of the cricoid cartilage.

Frequency and Age. There were 2744 cases of neoplasia of the oropharynx and hypopharynx contained in the AFIP-OTR material contributed between 1939 and 1976, and accounted for 13 percent of all upper respiratory and temporal bone neoplasia in the AFIP-OTR during those years. Eighty-nine percent were mucosal keratinizing squamous cell carcinomas of varying differentiation. Cunningham and Catlin, reporting 164 patients in Memorial Sloan-Kettering Cancer Center, noted 81 percent were men and 19 percent were women. Jacobsson reported that in Sweden 60 percent of mucosal squamous cell carcinoma of the hypopharynx occurred in women. He also reported that the percentage of women with hypopharyngeal cancer in Scotland was 55 percent; Norway, 50 percent; Ireland, 40 percent; and France, 1 percent. Age in the United States ranged from 40 to 85 years, with 88 percent being older than 50 years of age (Cunningham and Catlin). Racial predilection has not been established. The overwhelming majority of patients are reported as smokers and alcohol imbibers.

Clinical. Dysphagia and sore throat are the common complaints, with lesser complaints of hoarseness and weight loss. Quite often (23 percent of patients according to Cunningham and Catlin), the presenting sign will be a neck mass representing a metastasis. The clinical staging suggested by the American Joint Committee on Cancer relied on size only in the oropharynx (T1, 2 cm diameter or less; T2, more than 2 cm, but less than 4 cm diameter; T3, more than 4 cm in diameter; and T4, massive tumor more than 4 cm in diameter, with invasion of bone, soft tissue of the neck, or deep musculature of the tongue). In the hypopharynx, the stage T1 neoplasm is localized to the site of origin (pyriform sinus, postcricoid area, or posterior pharyngeal wall). Stage T2 is the extension of neoplasm to adjacent region or site without fixation of the larynx, while stage T3 is the similar extension, with fixation of the larynx. Stage T4 signifies massive tumor invading bone or soft tissue of the neck. In the series of 162 cases of hypopharyngeal mucosal carcinomas, Carpenter and associates noted 72 percent originating in the pyriform sinus, 23 percent in the posterior pharyngeal wall, and 5 percent in the postcricoid region. In their series, 67 percent of patients had cervical adenopathy on initial examination, suggestive of metastatic disease.

Gross and Microscopic. The gross description of hypopharyngeal and oropharyngeal mucosal squamous cell carcinomas is that of a fungating, ulcerative, gray to pink-red neoplasm that may measure up to several centimeters in diameter. The histology is that of the keratinizing squamous cell carcinoma. The Broders' histologic grade in the 162 patients with hypopharyngeal mucosal carcinomas of Carpenter and associates was grade I or II, 27 percent; grade III, 60 percent; and grade IV, 13 percent.

Treatment and Prognosis. Carpenter and colleagues found that survival rates in patients with hypopharyngeal mucosal carcinoma did not vary whether surgery alone or a combination of surgery with preopera-

tive radiation was employed; however, patients treated by radiation alone had a poorer survival. Their overall three-year survival was 52 percent and overall five-year survival was 47 percent. Cunningham and Catlin, in their patients with cancer involving the oropharynx and hypopharyngeal posterior and lateral walls, felt combination surgery and planned radiation therapy offered the best survival, with irradiation alone considered generally ineffectual. Their overall five-year cure without evidence of residual disease was 21 percent.

SQUAMOUS CELL CARCINOMA OF THE LARYNX

Frequency and Age. Keratinizing squamous cell carcinoma accounts for 99 percent of mucosal carcinoma of the larynx, with the remaining 1 percent containing the undifferentiated oat cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma. The latter two entities will be discussed later with adenomatous neoplasia of the upper respiratory tract. The AFIP-OTR, between 1939 and 1976, accessioned 8835 cases of laryngeal neoplasia and 71 percent (6273) were squamous cell carcinomas. In Putney and Chapman's 311 patients with laryngeal cancer, 96 percent were males and 4 percent were females. Patients in their series ranged in age from 33 to 83 years, with the mean being in the fifth decade. A rare childhood squamous cell carcinoma is cited.

Epidemiology and Etiology. Decker and Goldstein list the major factors for cancer of the larynx as tobacco and alcohol. Apparently the Syrian hamster is a unique animal model that has experimentally confirmed a linear dose-response effect of tobacco smoke and a promoting influence of ethanol in producing a sequence of laryngeal mucosal hyperplasia to dysplasia to invasive carcinoma histologic changes. Glottic mucosal carcinoma is apparently related to smoking, while extraglottic carcinoma of the larynx is linked to ingested agents (alcohol). Other factors suggested but not definitely proved as a direct cause are socioeconomic, geographic, vocal stress, racial, asbestos, nickel, mustard gas, and isopropyl alcohol manufacture (Chovil).

Clinical. The clinical grading of squamous cell carcinoma of the larynx is related to the three anatomic areas of the organ: the glottis (true vocal cord); the supraglottis (including the epiglottis, ventricular bands, arytenoids); and the subglottis. A stage T1 neoplasm is confined to one anatomic area with normal organ mobility; stage T2 neoplasm involves two or three adjacent anatomic areas, but with normal organ mobility; and stage T3 neoplasm, besides having the surface involvement of stages of a T1 or T2, has deep laryngeal involvement, vocal cord fixation, extension to the postcricoid area, to the pyriform sinus or pre-epiglottic space, or a combination. A stage T4 neoplasm extends beyond the laryngeal anatomic boundaries.

Hoarseness was the presenting sign in 94 percent of the 311 patients reported by Putney and Chapman. Less frequent events, such as respiratory airway obstruction, throat pain, dysphagia, or hemoptysis, indicates an advanced laryngeal involvement. Carcinomas arising from the supraglottic area will usually be more advanced before becoming symptomatic. In 500 patients with laryngeal and pyriform sinus carcinoma reported by Kirchner and Owen, 209 (42 percent) were glottis in origin; 97 (20 percent) were supraglottic; 10 (2 percent) were subglottic; 64 (12 percent) were transglottic; and 120 (24 percent) arose from the pyriform sinus. One percent of

Kirchner and Owen's series of patients with stage T1 glottic carcinomas (209) presented with regional neck or lymph node metastases, while 8 of 73 patients with stage T2 and T3 glottic carcinoma manifested neck metastasis. Over half their patients with pyriform sinus carcinoma developed regional neck or lymph node metastases. In 96 patients with laryngeal carcinoma treated by primary en block laryngectomy and radical neck dissection, McGavran and associates found cervical lymph node metastases in 19, 33, and 52 percent of subglottic, supraglottic, and transglottic involvement, respectively

Daly and Strong noted synchronous or metachronous second primary neoplasms in 19.5 percent of 535 patients with glottic carcinoma.

Gross. The majority of squamous cell carcinoma of the larynx varied from 1 to 4 cm in diameter (McGavran et al.) (fig. 81). They are most often described as a fungating, pink to gray mass, with central ulceration being common. Surrounding laryngeal induration in larger tumors is expected. Rare presentations are papillomatous in appearance, in which case the histology is necessary to confirm the malignant nature.

Microscopic. Utilizing a histologic grading system of well differentiated, moderately differentiated, and poorly differentiated squamous cell carcinoma, McGavran and associates, in 96 laryngectomy specimens containing squamous cell carcinoma, found 9 percent well differentiated, 48 percent moderately differentiated, and 43 percent poorly

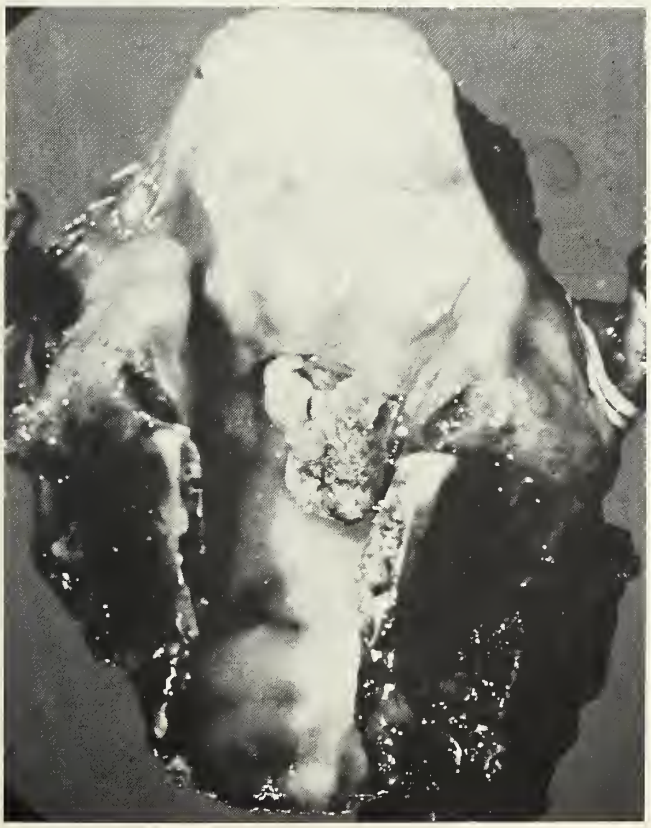

Figure 81
SQUAMOUS CELL CARCINOMA
A gross specimen of squamous cell carcinoma of the larynx.

differentiated squamous cell carcinomas. Chung and associates, in a study of 73 patients, found that glottic squamous cell carcinomas were well and moderately differentiated pathologically. Supraglottic lesions were more likely to be moderately and poorly differentiated, and subglottic lesions would be poorly differentiated squamous cell carcinomas (figs. 82, 83). They also confirmed that the smaller the primary laryngeal carcinoma, the more differentiated the histology. Sessions correlated the histologic differentiation of laryngeal squamous cell carcinoma directly to regional lymph node metastases, with well differentiated neoplasms less likely to metastasize than undifferentiated neoplasms.

Small cell or oat cell carcinomas have been recorded arising in the larynx. Gnepp and associates, in their review of the subject, studied 20 patients. The neoplasm is typically composed of anaplastic small cells with scanty cytoplasm and a relatively large hyperchromatic oval or triangular nuclei (figs. 84, 85). Mitoses were plentiful and occasional alveolar formation was noted among the cells. Electron microscopic examination revealed intracytoplasmic neurosecretory gran-

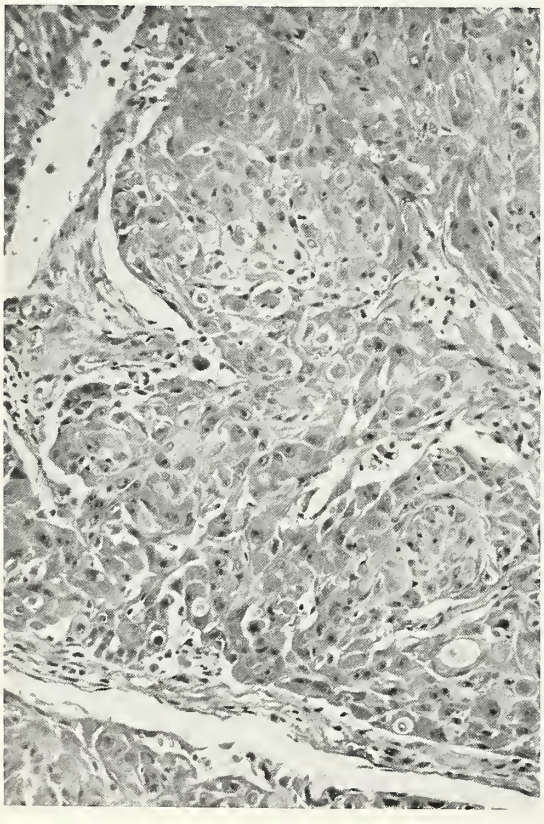

Figure 82
SQUAMOUS CELL CARCINOMA
This moderately differentiated squamous cell carcinoma of the larynx is from a 55 year old man. X160.

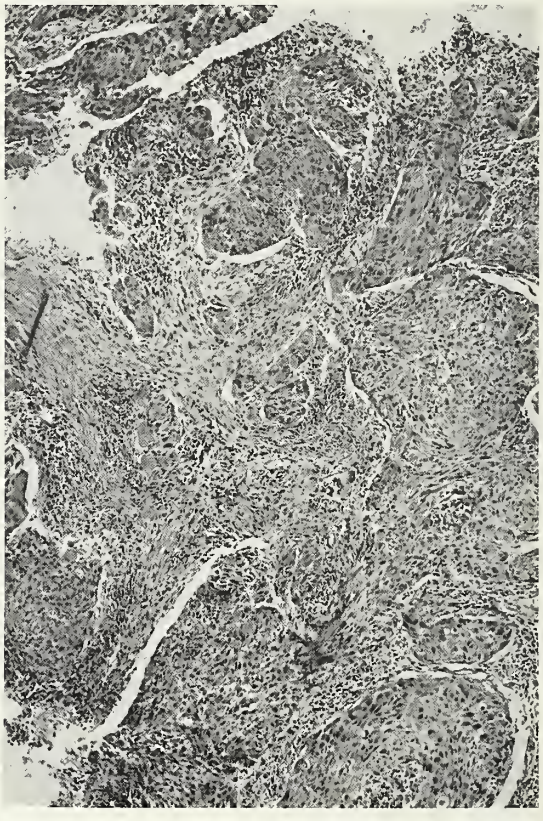

Figure 83
SOUAMOUS CELL CARCINOMA
This poorly differentiated squamous cell carcinoma with a prominent desmoplastic reaction is from the larynx of a 68 year old woman. X63.

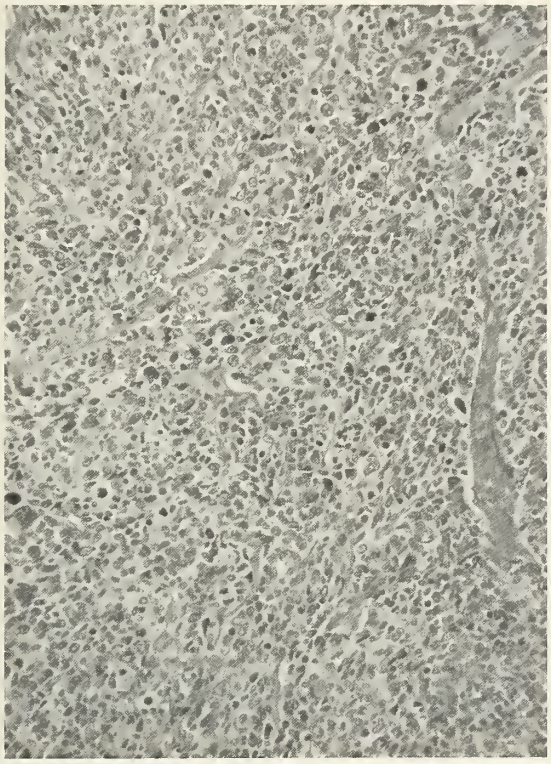

Figure 84
(Figures 84 and 85 are from the same patient)
SMALL CELL CARCINOMA
A small cell (oat cell) carcinoma infiltrating the laryngeal submucosal tissue. The neoplastic element is composed of numerous round and oval hyperchromatic cells with minimal cytoplasm. (Fig. 2A from Gnepp, D.R., Ferlito, A., and Hyams, V.J. Primary anaplastic small cell (oat cell) carcinoma of the larynx. Cancer 51:1731-1745, 1983.) X100.

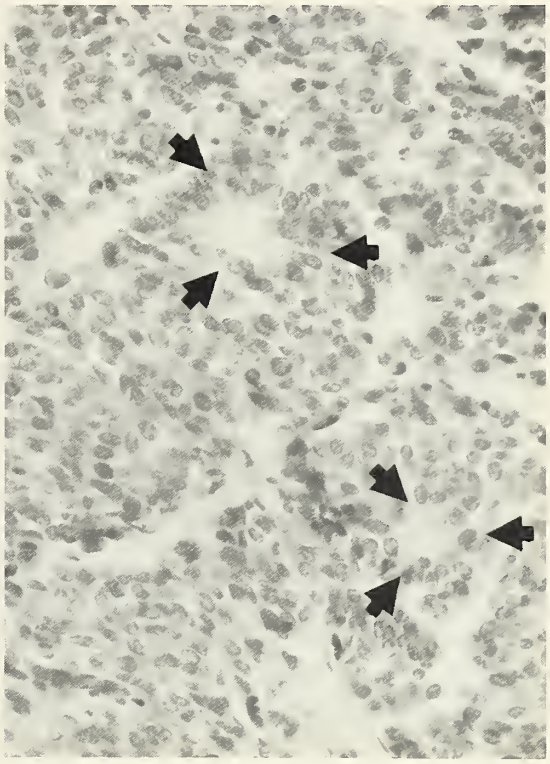

Figure 85
SMALL CELL CARCINOMA
Higher magnification of a different microscopic area in the neoplasm in figure 84 shows typical rosettes (arrows), but they are infrequent in the small cell carcinoma. X200. (Fig. 3 from Gnepp, D.R., Ferlito, A., and Hyams, V.J. Primary anaplastic small cell (oat cell) carcinoma of the larynx. Cancer 51:1731-1745, 1983.)

ules similar to those found in the oat cell carcinomas of the lung, leading to the assumption of origin from Kulchitsky-like cells present in the larynx.

According to Thomsen and associates, exfoliative cytology has not proven to be of benefit in diagnosis of laryngeal carcinoma.

Treatment. Complete agreement on the therapeutic approach for squamous cell carcinoma of the larynx has not been reached, but for the most part the clinical stage T1 and T2 lesions have been successfully treated by radiotherapy, while the advanced clinical stages T3 and T4 have had better overall results from primary surgical removal, with or without postoperative radiation. Combination surgery and radiation has proved advantageous in the advanced stages of laryngeal squamous cell carcinoma and, especially, the small cell or oat cell carcinoma (Gnepp). Chemotherapy has as yet to be satisfactorily evaluated in treatment of carcinoma of the larynx.

Prognosis. There is a linear relationship between the clinical staging and five-year survival. A compilation of 23 medical centers throughout the world, presented at the Centennial Conference of Laryngeal Cancer at

Toronto in 1974 (Kagan), revealed that for treated glottic carcinoma, the five-year survival was 72, 59, 45, and 61 percent for T1, T2, T3, and T4 lesions, respectively. Of the 20 patients with small cell or oat cell carcinoma primary in the larynx, Gnepp and associates noted only 4 of 19 patients were alive at the time of 1 year; 15 months; 2.5 years; and 7.5 years following diagnosis and treatment. The mean length of survival following diagnosis of those patients who succumbed was 7.9 months.

SQUAMOUS CELL CARCINOMA OF THE TRACHEA

Squamous cell carcinoma is the most frequent malignant neoplasm arising in the trachea. In the AFIP-OTR material from 1939 to 1976, squamous cell carcinoma represented 80 percent of all primary malignant neoplasms in 550 patients with tracheal malignant neoplasia. The highest incidence occurred in the 40 to 60 year age group, with males affected at least twice as often as females (Heffner). Stridor, cough, hemoptysis, and hoarseness are the common symptoms. Approximately 60 percent of squamous cell carcinomas occur in the lower third of the trachea, 30 percent in the upper third, and 10 percent in the middle third. Most often the gross lesion is polypoid, with the average size quoted as 4 cm (Heffner). A rare oat cell or small cell carcinoma is reported. Metastases, regionally and distally, are common, with the paratracheal and cervical lymph nodes, esophagus, and mediastinum the most common areas of spread. Treatment of squamous cell carcinoma of the trachea is hampered by the advanced tumor state at the time of diagnosis and the technical difficulty in removing large segments of the trachea with a successful subsequent reanastomosis. Radiation has been essentially palliative. Kurien and Cole reported a five-year 4.4 percent survival rate in 45 patients with squamous cell carcinoma of the trachea.

VERRUCOUS SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY TRACT

SYNONYMS AND RELATED TERMS: Verrucous carcinoma; verrucous cancer; Ackerman's tumor.

Definition. Verrucous squamous cell carcinoma is a verrucoid, highly differentiated, squamous cell carcinoma of mucosal or skin surfaces, with a tendency for prominent surface keratin production, and with locally destructive, but not metastatic, capabilities.

Frequency and Age. The neoplastic entity is recorded as occurring most often in the oral cavity (4 percent of all carcinoma occurring in the oral cavity [Dockerty et al.]). The next most common site is the upper respiratory tract, where the majority of verrucous squamous cell carcinomas arise from the laryngeal glottic area. In approximately 6500 patients with squamous cell carcinomas involving the larynx recorded in the AFIP-OTR data between 1939 and 1976, only .7 percent were diagnosed as verrucous squamous cell carcinoma. Ferlito and Recher recorded a 3.42 percent verrucous carcinoma diagnosis among 2398 primary and recurrent malignant neoplasms of the larynx and hypopharynx between 1965 and 1979. In 39 patients with verrucous squamous cell carcinoma of the upper respiratory tract recorded in the AFIP-OTR (28 larynx, 11 sinonasal and nasopharynx area), patient ages ranged from 37 to 77 years, with a mean of 60 years. In the younger individuals, extralaryngeal sites were favored. There were 35 males and 4 females. In the Ferlito and Recher series of laryngeal verrucous squamous cell carcinoma, re-

ported ages were between 29 and 76 years in 74 men and 3 women, with a median age of 58 years.

Etiology. Although tobacco chewing and the oral use of snuff has been implicated in oral cavity verrucous squamous cell carcinoma, this habit cannot very well be implicated in the upper respiratory tract. Biller and associates identified only one nonsmoker in reporting 15 cases of verrucous squamous cell carcinoma of the larynx. Viral etiology cannot be completely eliminated, although no viral particles are seen within the neoplasm (Prioleau et al.).

Clinical and Gross. The typical gross description is that of a pale, warty, fungating, locally aggressive, ulcerated mass. The neoplasms are usually attached by a broad base and they vary in size, possibly covering several centimeters in area. The symptoms are somewhat prolonged, with hoarseness being most prevalent in the larynx, dysphagia in the pharynx, and obstruction in the sinonasal tract. Obstruction of the airway in any upper respiratory tract site was not unusual. In the larynx, as shown by both the AFIP-OTR material and the literature, approximately 90 percent of the laryngeal verrucous squamous cell carcinomas originate on the true vocal cord. In the pharynx, any area is susceptible, while in the nasal cavity, the anterior half is usually the area involved. Regional lymph node enlargement is not a part of the symptoms complex unless due to inflammation. The AFIP-OTR material contains no patients with head and neck verrucous squamous cell carcinoma manifesting regional or distant metastasis.

Microscopic. The characteristic histologic finding is a uniformly benign-appearing, essentially nonanaplastic, nonmitotic squamous cell tumor (figs. 86-88). The squamous neoplastic proliferation may consist of surface papillary fronds ("church spires") capped by marked surface hyperkeratosis (fig. 86). Occasionally, the squamous cell element may extend into underlying submucosal stroma as keratin filled cystlike structures. Another significant microscopic characteristic is the broad, rounded, pushing border. There is no single-file cellular invasion of neoplasm. Chronic inflammatory cells may be profuse in adjacent stroma, sometimes obscuring the squamous borders and giving an illusion of tumor invasion. Microabscesses may occur in neoplastic epithelium and giant cell foreign body granulomas can be seen in the submucosa, apparently a reaction to excess keratin production. If the verrucous squamous cell carcinoma has reached a sufficient size and invasiveness, the uniform, well differentiated squamous tumor cords will cause pressure

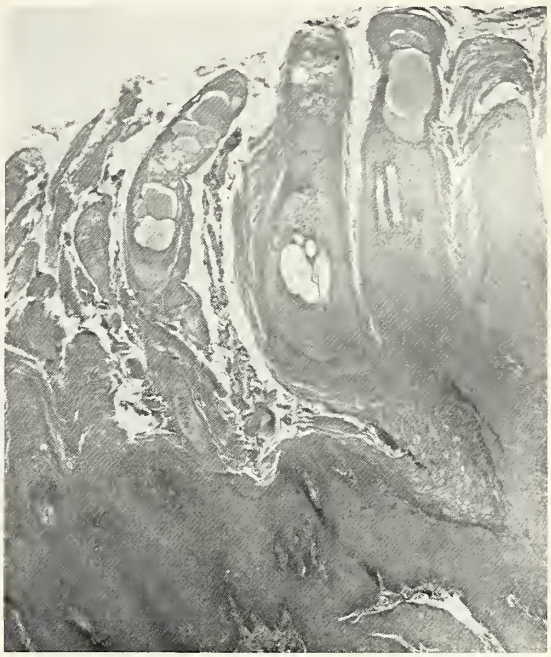

Figure 86
VERRUCOUS SQUAMOUS CELL CARCINOMA
This scanning power magnification of a verrucous carcinoma of a laryngectomy specimen demonstrates the "church spire" surface keratosis. X25.

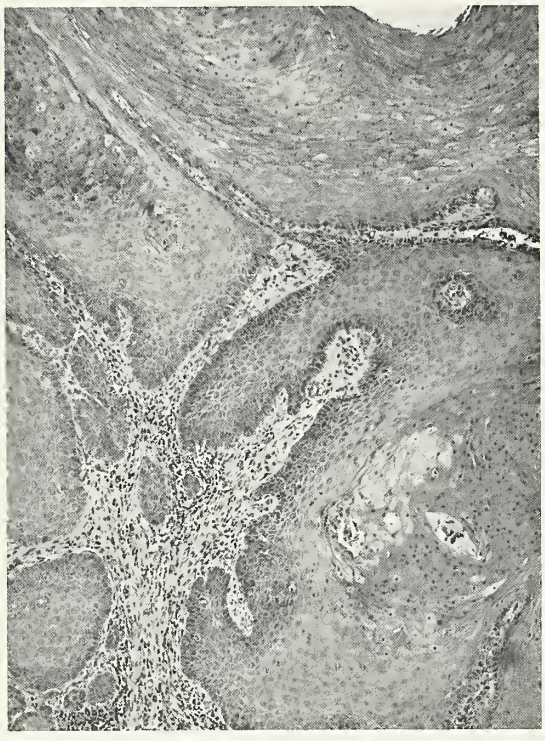

Figure 87
VERRUCOUS SQUAMOUS CELL CARCINOMA
A verrucous carcinoma of the larynx with the necessary microscopic changes, such as surface hyperkeratosis, uniform squamous neoplastic proliferation, and a rounded tumor peg infiltration. X160.

necrosis of any adjacent cartilage or bony structures.

On electron microscopic study, verrucous squamous cell carcinoma has all the features of well differentiated squamous cell carcinoma, with an overall architecture resembling normal epidermis (Prioleau et al.). Autoradiographic study by Prioleau and associates revealed the presence of a thick layer of nonproliferating, nonkeratinized cells between the basal germinative layers and the surface. This resembled normal epidermis or squamous mucosa and has not been identified in other types of conventional squamous cell carcinomas. Immunofluorescent findings revealed, in general, a basement membrane present in all sections of the tumor, which tended to follow blunt, bulbous rete pegs, although in places it has a disorganized, spiky configuration.

Differential Diagnosis. In no other upper respiratory neoplasm is there greater need for cooperation between surgeon and pathologist than in the diagnosis of verrucous squamous cell carcinoma. In the consultation experience of the AFIP-OTR, the main diagnostic difficulty was the separation of well differentiated conventional squamous cell carcinoma from the verrucous squamous cell carcinoma. The recognition of epithelial (squamous cell) atypia and dysplasia and the invasion by single and small groups of neoplastic squamous cells should aid in delineating the former. Rarely, a laryngeal biopsy specimen will reveal a superficial portion of an exophytic lesion consisting of uniform squamous epithelial proliferation with prominent surface keratinization that is assumed to be a verrucous squamous cell carcinoma, but when the entire lesion is surgically removed, additional histologic areas will support the more anaplastic conventional squamous cell carcinoma. On a partial biopsy specimen, when the clinical and histologic appearances support a diagnosis of verrucous squamous cell carcinoma, one would be wise to add "consistent with" to the diagnosis and remind the surgeon that a histologic examination of the entire surgically-removed lesion is necessary for a reliable verrucous squamous carcinoma diagnosis.

The second common differential diagnostic problem is distinguishing between a simple benign laryngeal mucosa hyperplasia with surface keratosis and verrucous squamous cell carcinoma. This can present a difficult decision and perhaps a quantitative clinical evaluation may be relied upon to determine whether the hyperkeratotic lesion

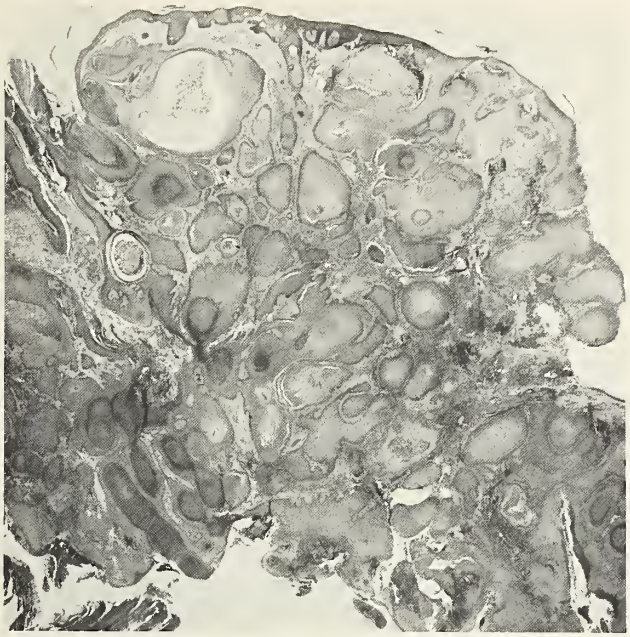

Figure 88
VERRUCOUS SQUAMOUS CELL CARCINOMA
This is an unusual microscopic pattern of a verrucous carcinoma of the larynx. The surface keratin is absent, but keratin is present in the underlying neoplastic mass. The clinical picture was that of a conventional squamous cell carcinoma. X25.

is diminutive enough to be considered just hyperkeratosis or is large enough to be diagnosed a verrucous squamous carcinoma.

Thirdly, there may be confusion between a simple keratotic squamous papilloma of the larynx and the laryngeal verrucous squamous cell carcinoma. Fechner and Mills recognized a lesion, usually arising from the true vocal cord, that they considered a verruca vulgaris. They delineated this mucosal surface lesion grossly as projecting above the mucosal surface without underlying stroma involvement and histologically having a remarkable resemblance to a pathology that might be considered by some as an early verrucous squamous cell carcinoma (fig. 89). Perhaps the safer decision would be to consider the so-called verruca vulgaris as an early verrucous squamous cell carcinoma with a recommended assured complete surgical removal, which at this small, early dimension should not cause any mutilating, debilitating laryngeal end results.

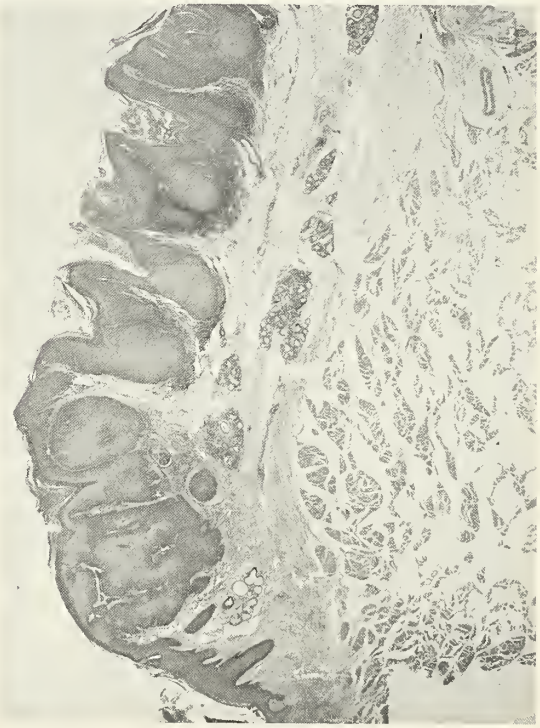

Figure 89
VERRUCOUS SOUAMOUS CELL CARCINOMA
In this scanning view, the possibility of a keratotic papilloma (verruca vulgaris) might be considered. X25.

Treatment. With a well established, highly differentiated squamous cell proliferation, one would feel that an assured surgical removal would be the undisputed treatment of choice; however, there are reports of successful management of laryngeal verrucous carcinoma by radiotherapy alone (Burns et al.). Several papers have told of anaplastic transformation of the neoplasm following radiotherapy, leading to rapid metastatic dissemination (Ferlito and Recher; Kraus and Perez-Mesa; Smith et al.). Ferlito and Recher also noted the tendency to develop a second malignant primary, especially a conventional squamous cell carcinoma, in the upper respiratory tract following radiation therapy for verrucous carcinoma. There are two cases of supposed verrucous squamous cell carcinoma of the larynx in the AFIP-OTR material reported as successfully treated with radiation alone, but histologic reexamination of the diagnostic biopsy material supported a diagnosis of well differentiated conventional squamous cell carcinoma.

Prognosis. Of the 28 cases of laryngeal verrucous squamous cell carcinoma reported from the AFIP-OTR, only one patient died of his disease, and this followed his refusal of surgical removal. In one case of sinonasal tract verrucous squamous cell carcinoma, the inability to completely remove the neoplasm led to recurrence and death by local aggression. Since the verrucous squamous cell carcinoma of the larynx is supposedly only a locally aggressive neoplasm, one should be able to select a conservative surgical approach when there is a choice. This may be followed by a recurrence, but such complication is probably not life threatening. Perhaps later more radical approaches may be utilized, but the patient has had the continuous use of his voice in the meantime.

SPINDLE CELL CARCINOMA OF THE UPPER RESPIRATORY TRACT

SYNONYMS AND RELATED TERMS: Spindle cell squamous cell carcinoma; sarcomatoid squamous cell carcinoma; pseudosarcoma; carcinosarcoma; collision tumor; Lane tumor.

Definition. A spindle cell carcinoma is a polypoid or fungating neoplasm which may infiltrate and metastasize. It is characterized histologically by foci of conventional squamous cell carcinoma associated with a transformation into a usually considerable amount of pleomorphic spindle cell histomorphology.

Frequency and Age. In the AFIP-OTR material between the years 1939 and 1976, 18 patients with spindle cell carcinoma were among 2800 total neoplasms of the sinonasal tract. Among these, 10 cases arose in the nasal cavity; 6 from the maxillary sinus; 1 from the frontal sinus; and 1 from the sphenoid and ethmoid sinuses (Howell et al.). Among approximately 5000 patients with pharyngeal neoplasms from the same time period, only 3 were diagnosed as spindle cell carcinomas. Among 6255 patients with squamous cell carcinomas of the larynx, 81 cases were diagnosed as spindle cell carcinoma, while in 436 patients with squamous carcinoma of the trachea, 2 were diagnosed spindle cell carcinoma. In the sinonasal cavity, the ages and sex distribution of the above groups revealed a span of 24 to 90 years (median 58.7 years), 14 men and 4 women. In the pharynx, the ages varied from 25 to 50 years, with all male patients, and in the larynx, the ages extended from 48 to 88 years, with a median of 68 years, 75 men and 6 women. The above statistics of age and sex agree with the comprehensive findings of Lambert and associates and Leventon and Evans.

Epidemiology and Etiology. In Leventon and Evans' series of 20 patients involving the oral cavity, pharynx, larynx, and sinonasal

tract, 18 indulged in the use of tobacco in some form; only 4 patients admitted to alcohol abuse. Six patients with invasive spindle cell carcinoma had been given irradiation therapy in the area of the spindle cell carcinoma sometime previously.

Histogenesis. The question of the true nature of this neoplasm has not been settled completely to everyone's satisfaction. Hyams has discussed the varying interpretations: (1) a squamous cell carcinoma with an atypical, but benign, accompanying spindle cell reactive process (pseudocarcinoma or Lane tumor); or (2) a collision or dual growth of a carcinoma and sarcoma (collision tumor, carcinosarcoma). The recent investigations (Leventon and Evans; Hyams) and those utilizing electron microscopic studies (Battifora; Lichtiger et al.) have supported the opinion that the spindle cell carcinoma represents a squamous cell carcinoma with the unique ability to present an anaplastic spindle cell metaplasia. Battifora has demonstrated histologic findings which suggest that the spindle cell component of a spindle cell carcinoma originates from mesenchymal metaplasia of squamous cells, thus helping to explain the rare finding of osseous or cartilaginous tissue in the neoplasm.

Clinical and Gross. In those cases of sinonasal tract involvement with spindle cell carcinoma, the presenting symptoms in descending order of frequency were nasal obstruction, epistaxis, nasal discharge, pain, deformity of sinonasal area, orbital symptoms, unilateral otitis media, and neck mass (Howell et al.). The pharyngeal neoplasms in the AFIP-OTR material caused mainly obstruction and dysphagia, while laryngeal involvement led overwhelmingly to hoarseness followed by airway difficulty. Pain and dysphagia were rare in primary laryngeal spindle cell carcinoma.

In the AFIP-OTR material, the sinonasal and nasopharyngeal spindle cell carcinomas were fungating, ulcerative, infiltrative tumors. Those cases arising from the lower pharynx, larynx, and trachea, however, had mainly a polypoid or exophytic appearance. Varying from 1 to 6 cm in diameter, these exophytic neoplasms appeared grossly to be covered by mucosa; however, histologic study often showed a complete denuding of any covering epithelial layer. As Leventon and Evans point out, the fungating ulcerating neoplasms usually have an aggressive course and poor prognosis. The polypoid or exophytic tumors can possibly have only superficial involvement and, hence, a better prognosis. However, some of the polypoid or exophytic group were capable of an aggressive and infiltrative behavior. In 39 patients with spindle cell carcinoma of the larynx, Hyams recorded 29 arising from the true vocal cord, 4 from the pyriform sinus, and the others from the supraglottic and subglottic areas. In this laryngeal group, four patients presented with later proven cervical lymph node metastases.

Microscopic. To be correctly diagnosed, the histology should reveal a conventional squamous cell carcinoma together with the spindle cell proliferation (figs. 90-92). In most instances, the spindle cell element dominates the tissue, but the occasional case requires a diligent search for the squamous component. In the polypoid lesions, the tumor surface is usually denuded of epithelium, with the possible exception of the junction of attachment to the normal mucosal surface. The squamous cell element, whether at the mucosal surface junction or within the tumor stroma, reveals a typical keratinizing squamous cell carcinomatous pattern of varying differentiation (fig. 90). In a rare case, the tumor surface is covered in part by a zone

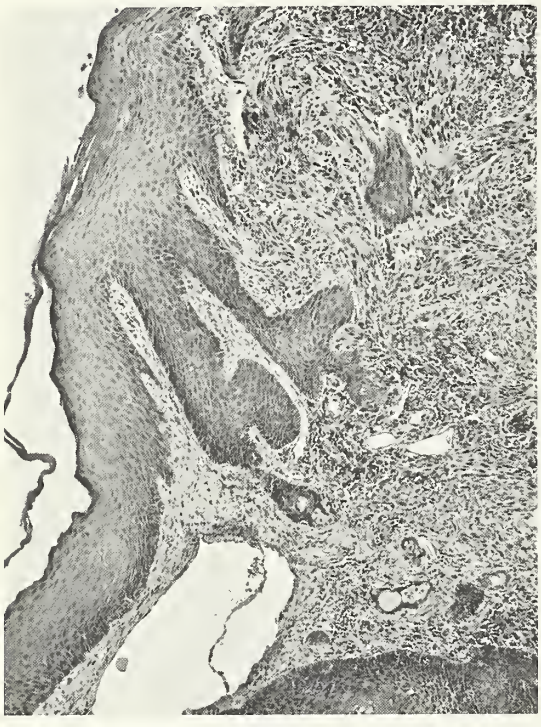

Figure 90
SPINDLE CELL CARCINOMA
This polypoid mass arising on the true vocal cord of a 62 year old man has a submucosal, malignant, spindle cell infiltration that is a spindle cell carcinoma. X63.

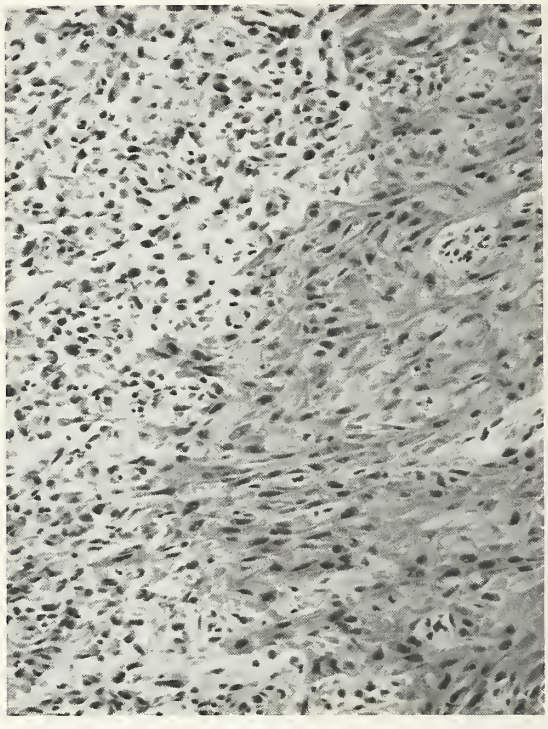

Figure 91
SPINDLE CELL CARCINOMA
Note the transition of the squamous cell carcinoma into the neoplastic spindle cell proliferation. X160.

of squamous cells in which the outer layers are histologically uniform and benign-appearing, but the inner or basal layers consist of dysplastic squamous cells, supporting the concept of a transition to the underlying malignant spindle cell elements (figs. 91, 92). The squamous cell carcinomatous portions often show a distinct demarcation from the surrounding cells; however, with some diligence, a transitional zone usually can be identified (figs. 93, 94).

The dysplastic spindle element of the spindle cell carcinoma which customarily dominates the histology is also variable in its composition. At one end of the scale can be an extremely cellular structure composed of abundant parallel bipolar spindle cells containing large round or oval nuclei with prominent single or multiple nucleoli and demarcated by saber-like bipolar cytoplasmic processes. Mitotic activity and nuclear pleomorphism varies. The architecture can reveal an anastomosing fascicular pattern reminiscent histologically of spindle cell sarcoma of mesodermal tissue origin. At the other end of the histologic spectrum can be spindle cell areas with a predominantly collagenous component and sparse spindle-shaped cells, but usually the nuclear atypia serves to differentiate these foci from a benign desmoplastic or reactive component. Occasional myxomatous foci can be identified. Multinucleated tumor cells may appear in varying numbers. The Masson trichrome stain consistently discloses an epithelial cell character of the cytoplasm of the spindle and

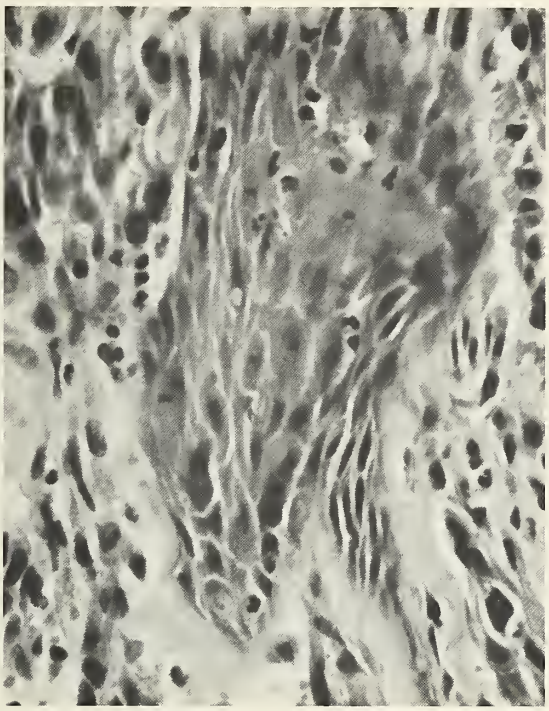

Figure 92
SPINDLE CELL CARCINOMA
A focus of squamous cell carcinoma in the center of a spindle cell carcinoma of the larynx, with transition of the carcinoma into a spindle cell morphology. X400.

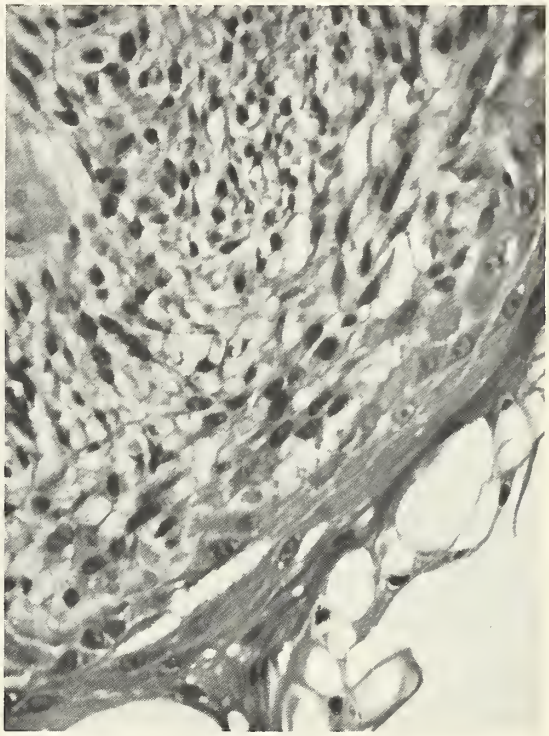

Figure 93
SPINDLE CELL CARCINOMA
A polypoid laryngeal tumor of a 65 year old man has an overlying squamous cell mucosa with the basal zone suggesting dysplasia and transition to the underlying malignant-appearing spindle cell element. X400.

giant cells with prominent appropriate staining of intercellular collagen. An antikeratin immunoperoxidase method may elicit a positive reaction in the spindle cells, particularly adjacent to typical squamous cell carcinoma histology. Electron microscopy demonstrates, in the spindle cell elements, some aggregates of keratohyalin and slender bundles of tonofilaments and occasional premelanosomes (Lichtiger et al.; Battifora). Desmosomes can also be demonstrated. In the AFIP-OTR data, these changes were better demonstrated close to the areas of definite squamous cell carcinoma micromorphology. In the AFIP material, approximately 5 percent of the cases of spindle cell carcinoma demonstrated dysplastic osseous tissue. In one case of nasopharyngeal neoplasm was an area of histologic chondrosarcoma, with the patient having a history of irradiation to the nasopharyngeal area for a previous conventional squamous cell carcinoma; however, not all the spindle cell carcinomas found with the dysplastic osseous tissue had a previous radiation exposure history. At this writing, neither osseous nor cartilaginous elements have been reported in a metastases. Hyams found the biphasic squamous cell carcinoma and malignant spindle cell element to be present jointly in regional lymph node metastases (fig. 95), putting to rest the idea that the spindle cell element is always a benign reactive infiltrate.

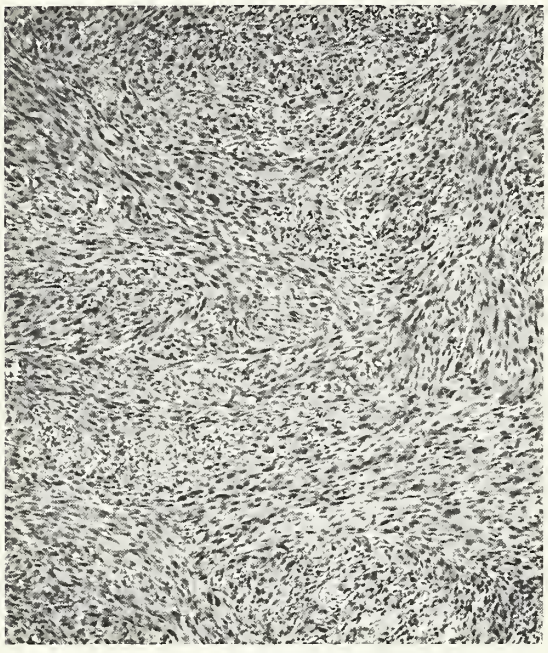

Figure 94
SPINDLE CELL CARCINOMA
This biopsy of a polypoid laryngeal mass has only a spindle cell micromorphology with no squamous cell element. Although this neoplasm was proved histologically to be a spindle cell carcinoma, this particular view makes it impossible to rule out a sarcomatous malignancy. X63.

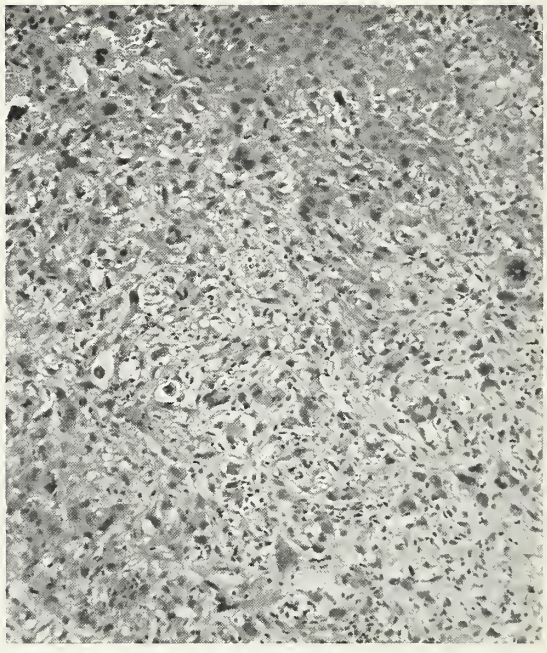

Figure 95
SPINDLE CELL CARCINOMA
A spindle cell carcinoma of the larynx metastatic to upper cervical lymph nodes contains both squamous cell carcinoma and spindle cell carcinoma. X160.

Differential Diagnosis. The difficulty is to separate the spindle cell carcinoma from spindle cell sarcoma. This problem is even more understandable when only the spindle cell morphology is noted in a biopsy. Light microscopy alone cannot rule out a sarcoma (fibrosarcoma and the like) on examination of only the spindle cell areas of the spindle cell carcinoma. In the upper respiratory tract, particularly the larynx and pharynx, sarcomas such as fibrosarcoma are rare and a diagnosis of spindle cell sarcoma or fibrosarcoma on a polypoid or fungating mass in this region should be made with caution until the entire neoplasm can be examined with multiple sections in order to search for the elusive squamous cell carcinoma element. The immunoperoxidase technics and electron microscopic examination are sufficiently informative to be recommended on a routine basis.

Occasionally an upper respiratory tract biopsy, particularly from the larynx, will reveal only an atypical spindle cell element in an otherwise polypoid connective tissue stroma background. The absence of a squamous cell carcinoma element precludes the diagnosis of a spindle cell carcinoma and these patients should have close clinical followup and, particularly, removal of any future suspicious clinical area for histologic evaluation. The lesion may represent a benign polypoid process with atypical spindle stroma cells. The possibility of an embryonal rhabdomyosarcoma is somewhat remote, considering the usual advanced age of the patients.

Treatment and Prognosis. Howell and associates, in 18 patients with the sinonasal tract spindle cell carcinoma, had only one surviving patient, who had been treated five years previously, primarily with surgery. There were an additional 9 patients treated by surgery alone, 6 patients treated with radiation therapy, and 2 patients treated with combination surgical and radiation therapy. All succumbed 6 to 41 months after diagnosis. Hyams found that 4 patients with laryngeal spindle cell carcinoma, treated solely by radiation, died of neoplasm within two years of diagnosis, whereas 12 of the remaining 16 patients were treated by surgery or combination surgery and radiation therapy and had survived over three years. Three patients with spindle cell carcinoma of the pharynx in the AFIP-OTR material were treated by a combination of surgery and radiation, and all died from tumor aggression. Lambert and colleagues, in their comprehensive analysis of laryngeal spindle cell carcinoma, felt that even the early T1 lesion should be treated with surgery. They observed that radiation therapy was associated with a high local recurrence rate. Leventon and Evans made the observation that those spindle cell carcinomas that were superficial responded well to surgery, whereas infiltrating neoplasms generally suffered a fatal outcome. Hyams noted that 3 of the 13 survivors with laryngeal spindle cell carcinoma underwent only a local surgical removal. At this writing, there has been no reported success utilizing chemotherapy as sole treatment for spindle cell carcinoma.

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NONEPIDERMOID EPITHELIAL NEOPLASMS OF THE UPPER RESPIRATORY TRACT

The ectodermally derived respiratory mucosa of the sinonasal tract and the endodermally derived mucosa of the pharynx and larynx give rise to similar nonepidermoid neoplasms. Compared to the statistically dominant squamous cell carcinomas, the nonepidermoid neoplasms make up only a small percentage of primary tumors in these sites. Nearly all the recognized epithelial neoplasms of the major salivary glands have a counterpart in the upper respiratory tract, but the malignant to benign ratio of adenomatous neoplasms in the sinonasal tract, pharynx, and larynx exceeds the benign by a margiń of 15 to 1.

Epidemiology. The epidemiology of all carcinomas of the sinonasal tract area differ from the types of carcinoma that arise from neighboring anatomic sites such as the nasopharynx. Sinonasal carcinoma has not been correlated with specific HLA types, nor is there evidence of strong genetic determinants for the sinonasal tract cancers. Epstein-Barr virus antibodies have been reported to be normal in patients with sinonasal carcinoma. On the other hand, strong correlates have been established for suspected carcinogens between occupational agents and sinonasal carcinoma, particularly those used in nickel and woodworking industries. Studies have clearly established that employees in nickel refineries are at significantly increased risk for development of nasal and pulmonary carcinomas. Nickel subsulphide and nickel oxide are especially carcinogenic (Robin et al.; Muir and Nectoux).

Airborne studies indicate dust particles are most easily deposited on the anterior part of the middle turbinate, the region of predilection for nickel-induced carcinoma. This region and the ethmoidal sinuses are also the sites of favor for the carcinomas found in woodworkers. A major difference exists, however. The nasal carcinomas found in nickel workers are squamous cell carcinomas; the nasal and ethmoid sinus carcinomas in woodworkers are predominantly adenocarcinomas. Not all sinonasal adenocarcinomas, however, are as clearly defined epidemiologically (Robin et al.).

CLASSIFICATION, FREQUENCY, AND SITES

The classification of the glandular nonepidermoid tumors of the upper airway can become quite complicated if glandular neoplasms are separated into salivary gland and mucosal origins. It is satisfactory to use the WHO classification of salivary glands (Thackray and Lucas) and combine this with a classification of surface mucosal tumors as in Table 1 (Batsakis). An abbreviated classification of adenomatous neoplasms of the sinonasal tract, pharynx (including nasopharynx), and larynx is presented in Tables 2, 3, and 4, together with the incidence of each entity in the AFIP-OTR data. In spite of its simplicity, the classification depicted in Tables 2, 3, and 4 functions satisfactorily in a clinicopathologic manner.

How many of these glandular nonepidermoid epithelial neoplasms of the upper respiratory tract derive from salivary gland structures is not determinable in the AFIP-OTR material. The pleomorphic adenoma (mixed tumor) seems a certainty to arise from a mucoserous salivary glandlike structure. All others, including the adenoid cystic carcinoma, could possibly originate from the

Table 1

CLASSIFICATION OF GLANDULAR NONEPIDERMOID TUMORS OF THE UPPER RESPIRATORY TRACT (Batsakis)

SALIVARY TYPE TUMORS	SURFACE MUCOSAL TUMORS
Benign	**Benign**
Pleomorphic adenoma	Papillary adenoma
Monomorphic adenoma	**Malignant**
Oncocytoma	Papillary adenocarcinoma
Malignant	Mucopapillary
Adenoid cystic carcinoma	Nonmucin producing
Mucoepidermoid carcinoma	Sessile adenocarcinoma
Acinous cell carcinoma	Mucin producing
Carcinoma ex pleomorphic adenoma	Nonmucin producing
Adenocarcinoma	Mucoid ("colloid") adenoma
Adenosquamous carcinoma	Special forms
Clear cell adenocarcinoma	Neuroendocrine adenocarcinoma
Undifferentiated carcinoma	"Colonic" type adenocarcinoma
	Undifferentiated adenocarcinoma

surface mucosa. There is a close embryologic relationship between the surface mucosa and the salivary glandlike submucosal mucoserous glands of the upper respiratory tract, since the latter arises from the surface mucosa by a process of invagination, branching, and functional modification (Batsakis et al., 1980). The distinction may be academic. The neuroendocrine adenocarcinomas referred to in Table 1 are those in which light microscopic appearance is that of adenocarcinoma.

The long interval between clinical symptoms and diagnosis also makes difficult a precise identification of site of origin. As will be seen below, several of the histologic types of nonepidermoid carcinomas have a clustering tendency to a given anatomic area of the upper airway. The adenocarcinomas usually arise high in the nasal cavity and ethmoid sinuses and the adenoid cystic carcinomas tend to arise in the maxillary antrum.

Table 2

ADENOMATOUS NEOPLASMS OF THE SINONASAL TRACT AFIP Otolaryngic Tumor Registry (1945-1975)

	No. Cases
Mixed tumor (1949-1974)	40
Adenocarcinoma, low grade	58
Adenocarcinoma, high grade	48
Adenoid cystic carcinoma	67
Mucoepidermoid carcinoma	11

Worsoe-Petersen, in a review of 2083 patients with sinonasal malignant neoplasia, found 112 adenocarcinomas (5.4 percent). Adenoid cystic carcinoma occurred at a slightly lower percentage than did adenocarcinoma, while mucoepidermoid carcinoma was noted in about 2 percent of all sinonasal malignancies. Robin and associates and

Table 3

ADENOMATOUS NEOPLASMS OF THE PHARYNX
AFIP Otolaryngic Tumor Registry (1945-1975)

	No. Cases
Oncocytic tumors	12
Mixed tumors	13
Pituitary type adenomas	7
Mucoepidermoid carcinoma	9
Adenoid cystic carcinoma	11
Adenocarcinoma	9

Table 4

ADENOMATOUS NEOPLASMS OF THE LARYNX
AFIP Otolaryngic Tumor Registry (1945-1975)

	No. Cases
Oncocytic tumors (1945-1969)	19
Mixed tumor	9
Mucoepidermoid carcinoma	12
Adenocarcinoma	26
Adenoid cystic carcinoma	16

Lewis and Castro independently found very similar incidence of adenocarcinoma among sinonasal malignant neoplasias.

PLEOMORPHIC ADENOMA

SYNONYMS AND RELATED TERMS: Mixed tumor; complex adenoma; pleomorphic sialadenoma.

Definition. Pleomorphic adenoma is a circumscribed tumor characterized microscopically by pleomorphic or mixed appearance. Clearly recognizable epithelial tissue is intermingled with tissue of mucoid, myxoid, or chondroid appearance (Thackray).

Incidence and Frequency. In contrast to its frequency in the major salivary glands, the pleomorphic adenoma (mixed tumor) is unusual in the upper respiratory tract. In the AFIP-OTR material, age of patients ranged from 3 to 82 years, with a median age between 40 and 46 years. There is apparently no sex preference in the sinonasal tract and larynx, but of 13 patients with pharyngeal pleomorphic adenomas, 11 were males.

Sites of Neoplasms. The nasal cavity is the most common area of involvement, with the nasopharynx and larynx distant followers. There is no documented case of paranasal sinus origin in the AFIP-OTR. In the 40 patients with nasal cavity mixed tumors that are reported by Compagno and Wong, approximately 80 percent arose from the bony or cartilaginous parts of the nasal septum. The remainder arose from the lateral wall and usually involved a turbinate. Their initial lack of aggressiveness is indicated by infrequent extension into the adjacent sinuses.

In the AFIP-OTR material, there were 5 tumors located in the nasopharynx and an additional 4 arose in the lateral wall of the oropharynx and hypopharynx. In the larynx, only 1 tumor was subglottic, with 8 cases supraglottic or epiglottic in origin.

Clinical. In the sinonasal tract the chief complaint was nasal obstruction and, less often, epistaxis. The patients usually sought medical attention within one year of onset of symptoms. In the pharynx, obstruction and the presence of a throat mass brought the patient to the physician. In the larynx, in order of descending frequency, the symptoms were hoarseness, pain, and dysphagia.

In the AFIP-OTR material, mixed tumors of the upper respiratory tract ranged from 0.7 to 7.0 cm. Typically, the mixed tumor is a

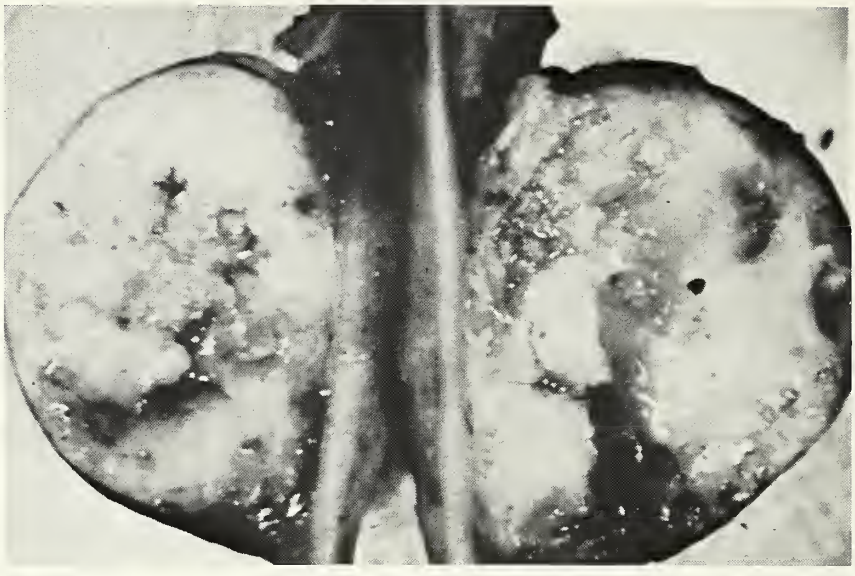


Figure 96
MIXED TUMOR
The demarcation of the neoplasm is obvious in this mixed tumor of the nasal septum.

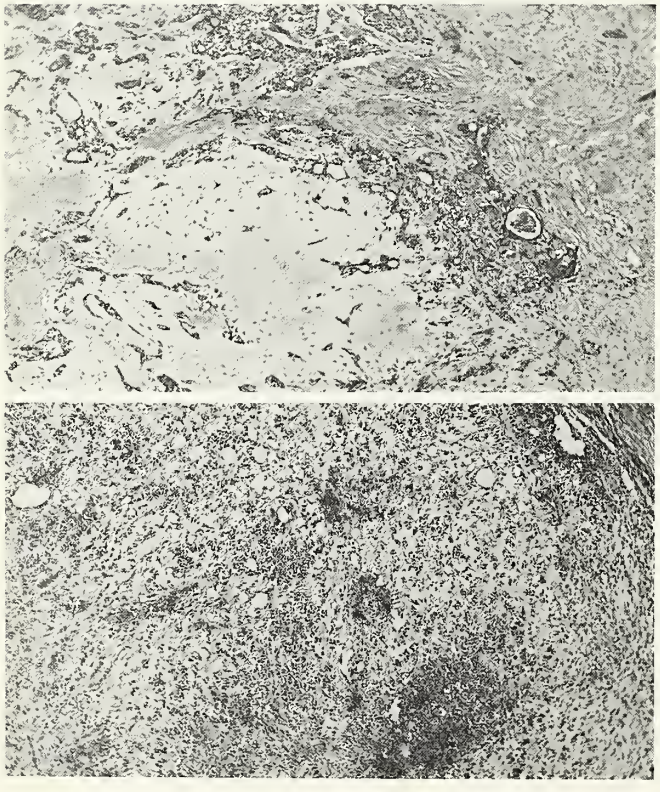


Figure 97
MIXED TUMOR
This mixed tumor presented as a pedunculated mass of the lateral wall in a 22 year old white woman. It had been present for eight years before excision. Contrast the pseudocartilaginous focus (above) with one of the more prevalent cellular foci (below). X40. (Fig. 1 from Compagno, J. and Wong, R.T. Intranasal mixed tumors [pleomorphic adenomas]. Am. J. Clin. Pathol. 68:213-218, 1977.)

homogenous, lobular mass (fig. 96), occasionally bosselated or cystic, but more often polypoid and translucent. Deviation from the usual gray-white appearance is most often due to hemorrhage.

Microscopic. Compagno and Wong have pointed out that the intranasal mixed tumor differs from its counterparts in the major salivary glands by a greater cellularity (figs. 97, 98). Epithelial elements rather than stromal elements predominate. At times, the tumors may be composed almost entirely of epithelial cells with little or no stroma. A similar greater cellularity was true also for the pleomorphic adenomas of the pharynx and larynx.

Differential Diagnosis. Grossly or clinically, the good demarcation from surrounding tissue of the usually solid neoplasm with strong suggestion of a capsule usually confirms the diagnosis of a benign mixed tumor. Microscopically, however, if the demarcation and encapsulation are not emphasized, the cellularity of the upper respiratory mixed tumor can be misleading and difficult to differentiate from adenocarcinoma, malignant mixed tumor, hemangiopericytoma, adenoid cystic carcinoma, and cartilage neoplasms.

Treatment and Prognosis. Local or total wide surgical excision usually prevents recurrences in the sinonasal tract as well as the pharynx and larynx. In 31 of the 34 patients with nasal cavity neoplasms followed by Compagno and Wong, there were no recurrences. The rarity of a myxoid stroma in intranasal mixed tumors has been cited as

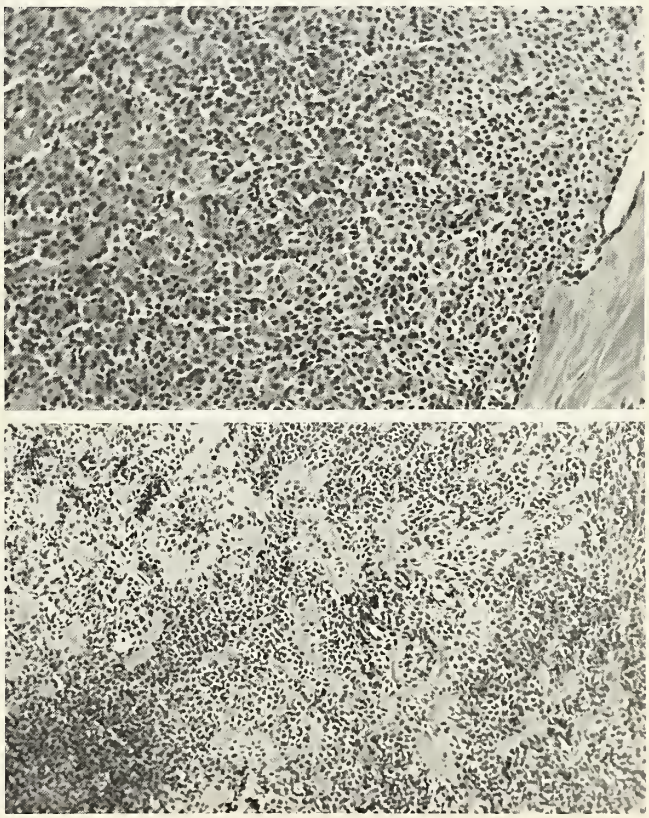


Figure 98
MIXED TUMOR
This mixed tumor presented as a multinodular and irregular mass located on the nasal septum. Note the cellularity. X100. (Fig. 2 from Compagno, J. and Wong, R.T. Intranasal mixed tumors [pleomorphic adenomas]. Am. J. Clin. Pathol. 68:213-218, 1977.)

a pathologic reason for the low recurrence rate. In the 10 percent of patients experiencing nasal cavity area recurrences, the lesion may extend into the paranasal sinuses. Recurrence may be quite delayed, appearing after the traditional five-year cure period. In the AFIP-OTR pharynx series, one patient died due to local growth six years following diagnosis and treatment by irradiation and chemotherapy. In the laryngeal group, one patient died two years following laryngectomy and radiation, due to extension of what was considered a questionable cytologic malignant mixed tumor.

The monomorphic (basal cell) adenoma, while relatively frequent in the minor salivary glands of the oral cavity, is an infrequent lesion of the upper airway, according to AFIP-OTR material.

CARCINOMA EX PLEOMORPHIC ADENOMA (MALIGNANT MIXED TUMOR)

Carcinoma ex pleomorphic adenomas arising from the mucoserous glands of the respiratory tract, according to AFIP-OTR records, are unusual and much less frequent than those arising in the oral cavity and major salivary glands. For the diagnosis, there must be clear evidence of benign mixed tumor associated with a malignant, usually carcinomatous component. In the study of the 40 patients of Compagno and Wong, there was no instance of carcinoma occurring in a previously benign pleomorphic adenoma anatomically situated in the sinonasal tract. Spiro and associates (1973) cite the maxillary antrum as a primary site for malignant mixed tumor in the upper airway. It appears that the malignant mixed tumor in this anatomic area is more aggressive and lethal than either adenoid cystic carcinoma or adenocarcinoma. One case of possible carcinoma occurring in a pleomorphic adenoma of the larynx is included in the AFIP-OTR data. Of interest are two patients originally listed in the AFIP-OTR as having mixed tumors of the nasopharynx. On followup, they were known to have died of local and distal spread of their neoplasms. When the slides were reviewed recently, the histologic diagnosis was changed to chordoma.

ONCOCYTOMA

SYNONYMS AND RELATED TERMS: Oxyphil adenoma; oncocytic metaplasia.

Definition. Oncocytoma is a benign tumor consisting of large cells with granular eosinophilic cytoplasm (oncocytes).

Lesions composed of oncocytes in the upper respiratory tract are, with few exceptions, a reactive or hyperplastic response to trauma or the aging phenomena. Solid tumors formed of oncocytic cells (oncocytomas) are rare in the airway (Cohen and Batsakis). The few examples reported have manifested an irregular, unencapsulated growth pattern and tend to invade locally, but rarely will be metastatic.

The oncocyte, whenever it occurs, possesses the same histologic and ultrastructural characteristics: acidophilic, granular cytoplasm, and numerous, often tightly packed, mitochondria (Johns et al.) (figs. 99, 100).

In the AFIP-OTR material, there were no distinct oncocytic neoplasms in the sinonasal tract, although a rare low-grade adenocarcinoma had a histologic suggestion of oxyphilic cytoplasm in the neoplastic cell. In the nasopharynx, even a small focus of oncocytic metaplasia may obstruct the eustachian tube with resultant otitis media. The diagnosis of oncocytic metaplasia of peritubal

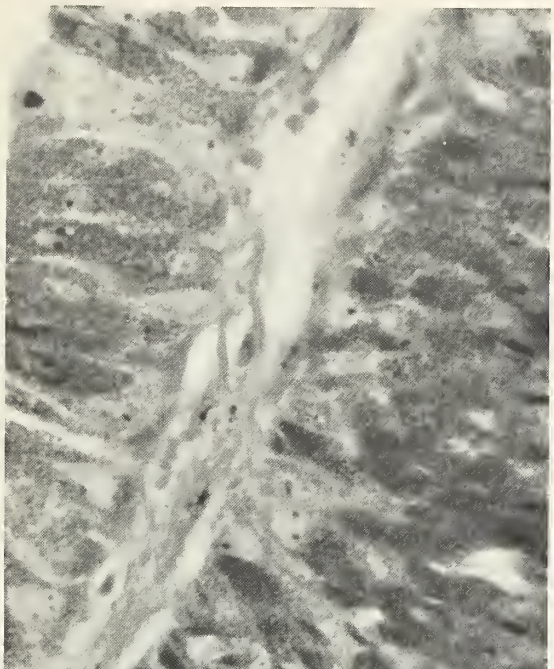


Figure 99
ONCOCYTIC TUMOR
A phosphotungstic acid hematoxylin (PTAH) stain demonstrates the granules of the cytoplasm. These granules represent pathologic mitochondria as seen in the electron microscopic illustration in figure 100. X800.

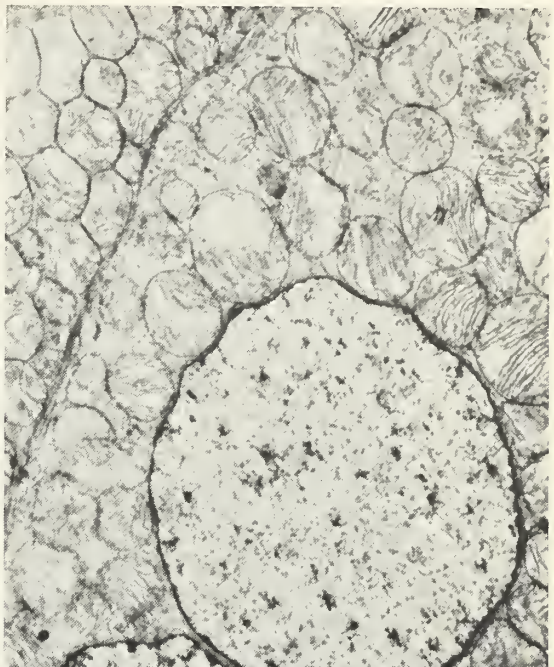


Figure 100
ONCOCYTIC TUMOR
An electron microscopic view of an oncocytic tumor with the characteristic engorgement of the cell cytoplasm by pathologic mitochondria. X12,000.

nasopharyngeal mucoserous glands must be considered in elderly patients presenting with small mucosal or submucosal nodules in the nasopharynx.

The vast majority of oncocytic lesions of the larynx in the AFIP-OTR experience are benign hyperplasia and not true neoplasms (fig. 101) (Holm-Jensen et al.; Gallagher and Puzon). Nearly all clinically significant lesions have been cystic. The ventricle and false cord are the sites of predilection (Table 5). In most instances, the oncocytic cysts are retention cysts, formed by ectatic excretory ducts. In the AFIP-OTR data, the mean age of patients with oncocytic cysts of the larynx has been 64 years, with an age range of 48 to 88 years. This age is analogous to the oncocytic tumors of major salivary tissue. Sex predominance varies from one series to another. On occasion, there may be an intense inflammatory reaction about the cyst. This has misled authors into considering them as Warthin's tumors. The Warthin's tumor is a lesion that has been restricted to the parotid gland. No unqualified example of a malignant oncocytic lesion occurring in the larynx has been recorded (Johns et al.).

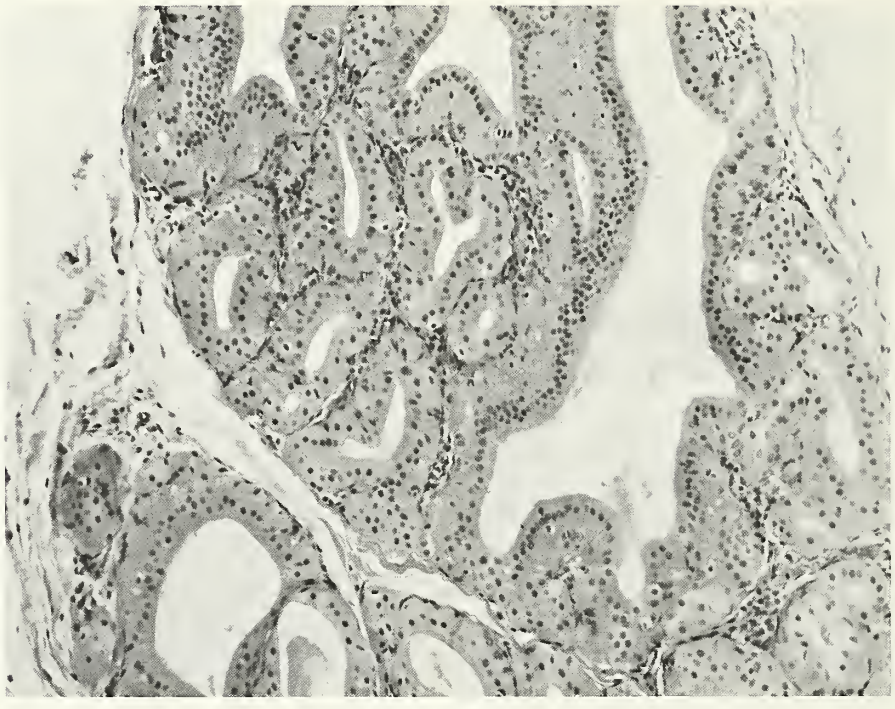


Figure 101
ONCOCYTIC CYST

This lesion, from the larynx, represents a benign oncocytic metaplasia of the supraglottic mucoserous glands. The uniform metaplastic cells contain an eosinophilic granular cytoplasm and a generally small, uniform, central nucleus. Occasionally, a double layer of metaplastic cells is seen, with the outer layer possibly myoepithelium. X160.

Table 5

ONCOCYTIC CYSTS OF THE LARYNX: SITES OF ORIGIN*

	No. Cases
Ventricle	43
Ventricular fold	19
Vocal cord	5
Anterior commissure	4
Subglottic	3
Arytenoid	2
Epiglottis	1
Not stated	1

*After Holm-Jensen et al.

ADENOID CYSTIC CARCINOMA

SYNONYMS AND RELATED TERMS: Adenocystic carcinoma. (The term cylindroma is used by some to designate the adenoid cystic carcinoma, but this terminology is ambiguous, since the term cylindroma is also utilized for a benign skin sweat gland adnexal neoplasm.)

Definition. Adenoid cystic carcinoma is an infiltrative malignant tumor having a characteristic micromorphologic cribriform appearance. The tumor cells are of two types, duct lining cells and cells of myoepithelial differentiation, and are arranged as small ductlike structures or larger masses of myoepithelial cells disposed around cystic spaces to give a cribriform or lacelike pattern.

Incidence and Frequency. There is agreement that this neoplasm is the most common

carcinoma of minor salivary tissue. Osborn, in a study of 1712 mucosal gland tumors of all types, found 557 or 32.5 percent were adenoid cystic carcinomas. Conley and Dingman report that 65 percent of all minor salivary gland tumors are malignant and that 38 percent are adenoid cystic carcinomas. Spiro and colleagues (1973) report a higher incidence of malignancy in their series of minor salivary gland neoplasms — 88 percent. Thirty-five percent of their 492 patients presented an adenoid cystic carcinoma. All these series were dominated by an oral anatomic location. Table 6 presents the anatomic distribution of 557 adenoid cystic carcinomas in the mucosal area of the head and neck.

Age and Sex Incidence. The age range of patients with adenoid cystic carcinoma in the upper respiratory tract begins in the third decade and extends into the ninth decade of life, with a peak incidence in the fourth to seventh decades. There is a definite male predominance, except in the pharynx, according to AFIP-OTR data.

Clinical. The clinical presentation of adenoid cystic carcinoma is not unique and may be duplicated by any of the mucoserous gland neoplasms. Lesions presenting in the antrum are associated with facial pain and swelling, and duration before diagnosis has ranged from months to four years. Over 50 percent of patients give a history of one year or more of symptomatology prior to diagnosis. Lesions involving the nasal cavity and nasopharynx have nasal obstruction, otitis media, and diplopia as common symptoms. The last is clear evidence of local extension. Larynx involvement is accompanied mainly by hoarseness, dyspnea, and cough.

Radiographic. Findings conform to what is usually found clinically and at the time of surgery (Dodd and Jing). In the paranasal sinuses, these consist of a soft tissue mass, usually extending beyond the confines of the sinus, with pressure erosion and destruction of the bony wall of sinus and invasion of surrounding structures.

Table 6

ADENOID CYSTIC CARCINOMA ANATOMIC SITE IN HEAD AND NECK*

Anatomic Site	Number of Adenoid Cystic Carcinomas	Percent of All Mucosal Gland Tumors at Site
Oropharynx		
Palate	210	29
Mouth	106	24
Tongue	124	54
Tonsil	34	26
Nose and Sinuses	113	37
Nasopharynx	48	54
Larynx	22	32
Trachea	11	82
Lacrimal Gland	20	50

*After Osborn, D.A.

Radiographic evidence of adenoid cystic carcinoma of the nasopharynx usually consists of a submucosal soft tissue mass arising from the superior posterior or lateral wall of the nasopharynx. In advanced cases, x-ray films will demonstrate extension to the clivus, sphenoid sinus, and floor of the middle cranial fossa. For demonstration of perineural spread of the neoplasm, tomography is imperative. The perineural spread is usually along the maxillary and mandibular divisions of the trigeminal nerve. In advanced cases, the foramen ovale and foramen rotundum may be involved with the extension of the tumor to the gasserian ganglion.

Gross. There are no distinguishing gross features. Most important is the difficulty of demarcating the tumor because of its insidious infiltrative growth. Spiro and associates (1974) report some fixation or extension to adjacent structures in some patients with the

primary lesion in the paranasal sinuses, nasal cavity, and pharynx. The firm, gray-white tumor in these anatomic areas is rarely less than 2 cm when diagnosis is made. In the larynx, the extent of the adenoid cystic carcinoma is usually underestimated by the clinician, as is proved by any attempt to surgically eradicate the tumor. The surgical pathology specimen will invariably reveal neoplastic extension through the surgical margins. In the AFIP-OTR data, the primary adenoid cystic carcinoma of the larynx was subglottic in origin in 6 patients and supraglottic in 10.

Microscopic. The tumor is composed principally of small, basal type cells. They may be arranged in cribriform pattern or appear in cords, a basaloid pattern, or glandular (tubular) form. An anaplastic variant occurs that may have somewhat larger, vesicular nuclei and distinct nucleoli, features not found in other types. The cribriform or "cylindromatous" type is most common and, in many instances, co-exists with one or the other variants. Brisk mitotic activity is never a feature except in the anaplastic types. Necrosis is conspicuously absent.

The typical cribriform appearance is due to the presence of numerous microcystic spaces that are pseudoluminal and lacking a definitive epithelial lining (fig. 102). They often contain a connective tissue mucin.

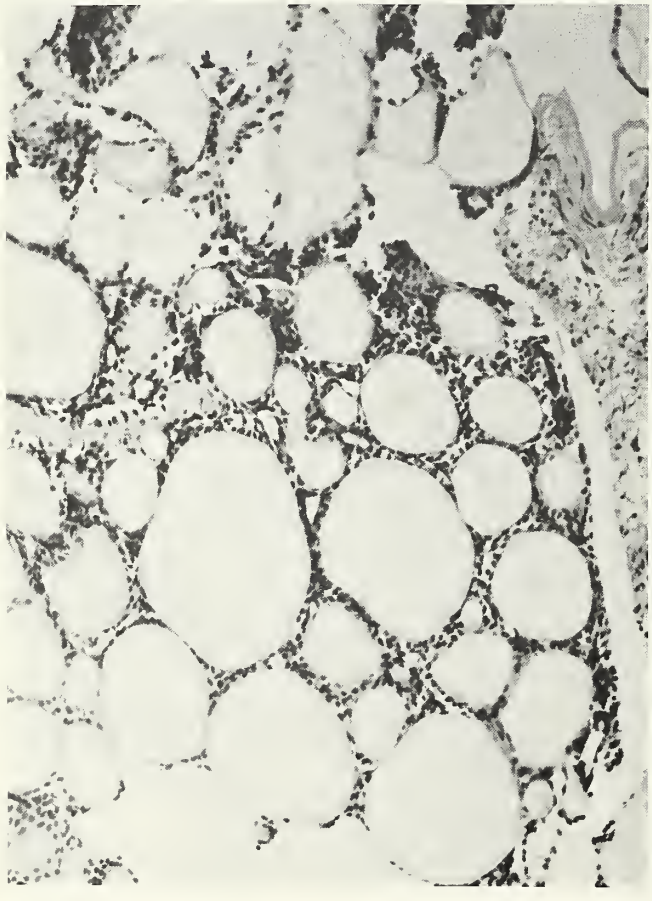


Figure 102
ADENOID CYSTIC CARCINOMA
Note the cribriform pattern of the adenoid cystic carcinoma, which emphasizes the small hyperchromatic cell that lacks orientation. There is a thin hyaline zone adherent to the outer portions of the cribriform lumen, another micromorphologic feature of this entity. X160.

These spaces lack microvilli, but frequently possess a basal lamina. Bordering cells frequently have desmosomal attachments. Sometimes the bordering cells contain filamentous bundles resembling tonofilaments or myofilaments.

True epithelial lined cysts may be found in nearly every form of adenoid cystic carcinoma, but are clearly outnumbered by the cribriform type. These tubular structures contain an epithelial type mucin (figs. 103, 104). Since they are true lumina, they are lined by microvilli.

The basaloid and anaplastic forms manifest a solid cellular growth (fig. 105) with a blunt or infiltrative invasion.

The stroma of the adenoid cystic carcinoma varies widely in amount and character. It ranges from scanty, loose connective tissue to a densely fibrous matrix. Occasionally, it is myxomatous. A frequent finding is hyaline material surrounding or surrounded by the basal cell component. The staining reaction of this material is variable and may show characteristics of collagen or exhibit a positive periodic acid-Schiff (PAS) reaction. The ultrastructural appearance is that of partly laminated, partly amorphous material. A common and almost identifying histologic finding is the spread of the adenoid cystic carcinoma to the perineural spaces or to the perineural lymphatics of adjacent peripheral nerves (fig. 105).

Prognosis. Although the authors of many published papers concerning adenoid cystic

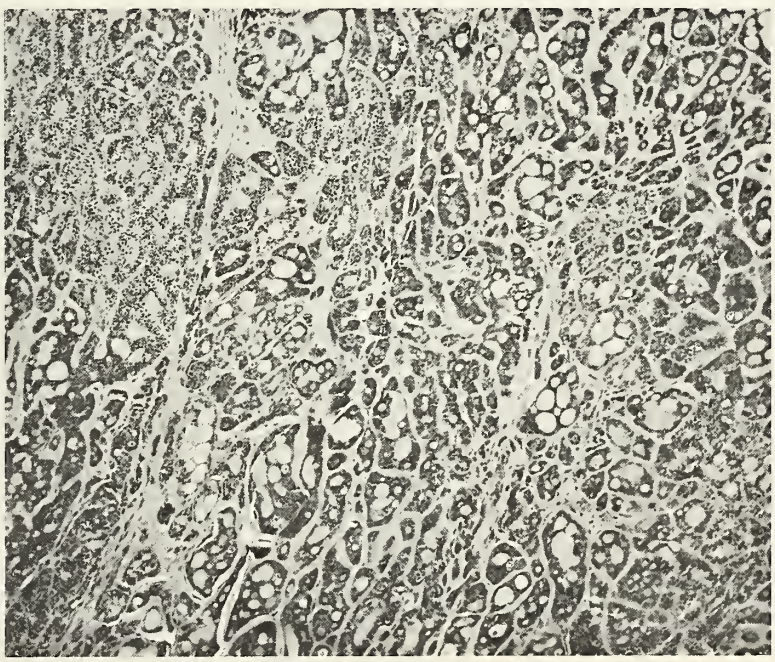


Figure 103
ADENOID CYSTIC CARCINOMA
This low power of an adenoid cystic carcinoma of the larynx suggests a combination of tubular and cribriform patterns. X63.

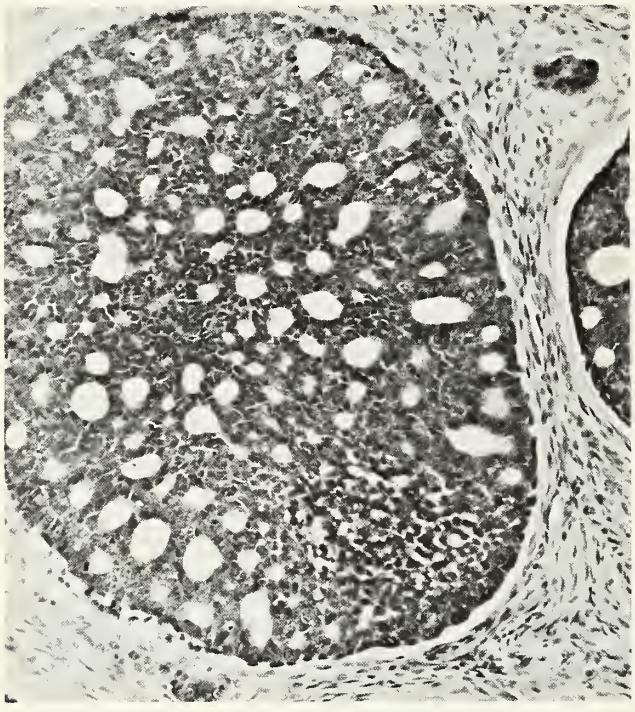


Figure 104
ADENOID CYSTIC CARCINOMA
In this so-called tubular type adenoid cystic carcinoma of the larynx, the neoplastic cell definitely is oriented around the lumen in a tubular fashion. X160.

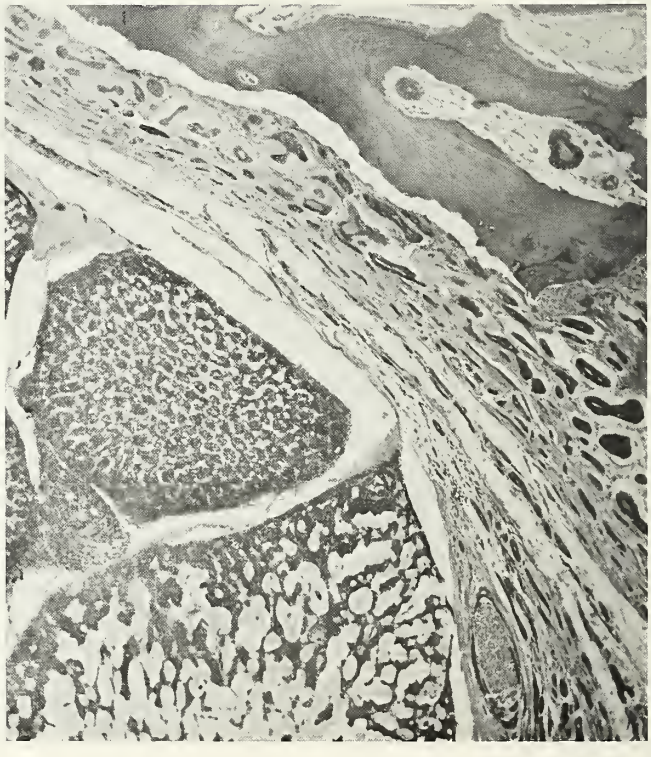


Figure 105
ADENOID CYSTIC CARCINOMA
This sinonasal tract adenoid cystic carcinoma exhibits an area of the so-called solid type, together with a tubular-cribriform pattern as well as areas of perineural space invasion and destruction of adjacent bone. X63.

carcinoma of the head and neck feel that there is no correlation of the variant histologic forms with a prognosis, Perzin and associates, in their series of head and neck adenoid cystic carcinomas, divided the neoplasm histopathologically into tubular, cribriform, or solid pattern and found survival was correlated as follows: tubular, a nine-year survival average; cribriform, an eight-year survival average; and the solid, a five-year survival average. Recurrences were 59, 89, and 100 percent for the tubular, cribriform, and solid type, respectively.

The biologic course, overall, of adenoid cystic carcinomas in the upper airway is one of relentless progression, local extension, persistence of neoplasm after attempted surgical removal, and death due to neoplasm. The life-consuming tendencies of the neoplasm are greatest in the airway. Spiro and colleagues (1979) related a 10-year determinate cure rate of only 7 percent in the nasal cavity, antrum, and larynx. This is compared to 29 percent for lesions of the parotid gland, 23 percent for oral carcinomas, and 10 percent for those in the submandibular gland.

Treatment. In spite of the dismal outlook for the adenoid cystic carcinoma of the upper respiratory tract, the majority of the medical literature recommends radical surgical treatment. Irradiation is certainly not curative, but may help control the neoplastic mass. Chemotherapy may also offer some relief in a generally hopeless tumor process.

Spread. Adjacent lymph node spread of adenoid cystic carcinoma of mucoserous gland origin plays a relatively minor role. Spiro and associates (1979) found 13.9 percent lymph node spread among 174 mucosal tumors — the lowest incidence of lymphatic spread in all types of malignant tumor in this anatomic area. Conley and Dingman, in their study of all head and neck adenoid cystic carcinomas, record a 16 percent metastatic spread to lymph nodes.

This low lymph node involvement contrasts sharply with a high hematogenous dissemination. As a rule, systemic involvement is associated with the unequivocal evidence of uncontrolled disease, whether at the primary site or in the neck. Spiro and colleagues (1979) report a remote spread of the adenoid cystic carcinoma in 40 percent of 174 patients. They further point out that adenoid cystic carcinoma accounted for 62 percent of distant metastases from all varieties of head and neck mucosal gland tumors.

The lungs, bones, and brain are the secondary metastatic foci of note. Distant metastases are accountable for but 10 percent of deaths due to the neoplasm. Extensive local growth is the usual cause of death.

ADENOCARCINOMA SINONASAL TRACT

Definition. Adenocarcinoma is a malignant epithelial tumor characterized by the presence of glandular structures.

These neoplasms arise from both the surface epithelium and the minor salivary gland tissue (Ranger et al.; Batsakis). Batsakis has pointed to the tendency of the adenocarcinoma to arise high in the nasal cavity and the ethmoid sinuses, as compared to the adenoid cystic carcinoma where the maxillary antrum and lower portion of the nasal cavity will more likely be involved. He has divided adenocarcinomas into basic clinicopathologic forms: papillary, sessile, and alveolar-mucoid. Included in this subclassification are those carcinomas that closely simulate colonic carcinomas. The latter tend to suggest arising from tissue that has a common origin with that of the gastrointestinal tract (Sanchez-Casis et al.). Argentaffin and

argyrophilic cells may be present in such tumors. This carcinoma, and very likely most of the adenocarcinomas of the sinonasal tract, arises from the pseudostratified columnar epithelial mucosa lining the airway with only the rare seromucinous gland origin.

Heffner and associates have divided adenocarcinomas of the sinonasal tract into a low- and high-grade classification. The former group contained an occasional suggestion of a salivary gland acinic cell carcinoma and even a rare cytology that resembled an oncocytic tumor, but the majority were made up of uniform cells forming well differentiated glandular structures or a papillary cystic conformation, or a combination of both. The high-grade category was composed of approximately half, with colonic, colloid, or combined glandular cell patterns. Nonspecific, poorly differentiated, glandular patterns, some with solid nests or sheets, constituted the other half.

Epidemiology. It has recently been pointed out that workers in footwear repair and manufacturing, wood, and furniture industries have increased risks of developing sinonasal cavity adenocarcinoma (Acheson et al.; Hadfield).

In 1965, a clinical study suggested a relationship between furniture making and sinonasal cavity adenocarcinoma in England (MacBeth). This association has been confirmed by epidemiologic studies in several areas of the world (Denmark, France, Belgium, and Australia) as well as the United States (Brinton et al.). Among furniture workers in England, the annual incidence for nasal and paranasal adenocarcinoma was 60/100,000, which approximated the rate for cancer of the bronchus in the general male population.

Brinton and associates, confirming earlier work, showed in their North Carolina study that a matched triplet analysis resulted in an odds ratio of 4.4 for furniture workers and 1.5 for other woodworking occupations. The excess risk among furniture workers was apparent below and above the age of 65 years. Twenty-four of the 37 deaths from nasal cancer in their study were said to be due to maxillary sinus primaries. Four of the 13 patients where the classification of the neoplasm was noted had adenocarcinoma.

Hadfield is to be credited with the most comprehensive study of the relationship of adenocarcinoma of the paranasal sinuses and woodworkers in the furniture industry. She studied 92 cases of carcinomas of the sinonasal tract in woodworkers in the furniture industry (34 squamous cell carcinomas, 35 adenocarcinomas, and 23 anaplastic carcinomas). For adenocarcinoma, the male-to-female ratio was 10 to 1. In all 35 patients with adenocarcinoma, the tumor appeared to originate in the ethmoid sinuses. In no patient with adenocarcinoma was there evidence of cervical lymph node metastases. Hematogenous spread was occasionally noted. Death was invariably due to intracranial extension of the neoplasm. The specific carcinogen still remains undetected.

Incidence. Males are afflicted more than females and the age of patients with adenocarcinoma of the sinonasal tract is not dissimilar to that of adenoid cystic carcinoma occurring in the same anatomic area. Heffner and associates presented 23 patients with a low-grade adenocarcinoma of the sinonasal tract, with even sex distribution. In high-grade adenocarcinoma of the sinonasal tract, 22 of the 27 patients were male.

Age. In 58 patients with well differentiated adenocarcinoma of the sinonasal tract contained in the AFIP-OTR, ages ranged from 9 to 90 years, with a median of 54 years. In poorly differentiated or high-grade adenocar-

cinomas of the sinonasal tract (48 patients), ages ranged from 15 to 84 years, with a median of 56 years.

Clinical. Early signs and symptoms are often innocuous and mimic benign disorders, such as nonspecific sinusitis, nasal obstruction, and nasal "stuffiness." Persistence of these and the advent of epistaxis leads to medical examination and, by this time, considerable extension of the neoplasm has occurred, i.e., invasion of bone and adjacent sinuses. Adenocarcinomas of the sinonasal tract, particularly the high-grade variety, have been likened to a "fire which smolders unnoticed within the walls of a house" (McDonald and Havens). When clinical and pathologic diagnosis is finally made, the disease may be beyond control.

Gross. The gross appearance varies from a relatively localized papillary or exophytic lesion to a sessile, poorly delineated tumor. A mucoid appearance may or may not be present.

Microscopic (figs. 106-112). Papillary adenocarcinoma may retain some cytologic identification with the mucosal epithelium and may be mucinous or only sparsely so. It is of interest that the mucinous papillary adenocarcinoma is the form most often associated with woodworking (Michaels and

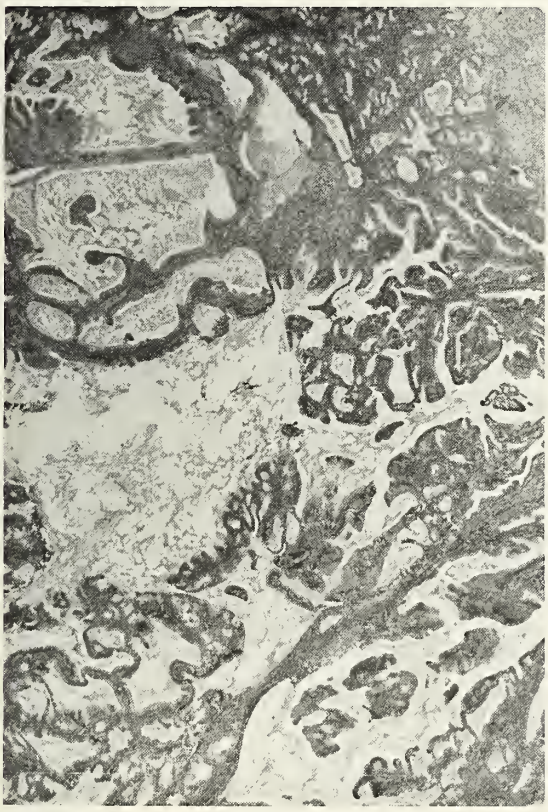


Figure 106
ADENOCARCINOMA
A scanning view of a low-grade adenocarcinoma of the sinonasal tract supports an architecture of a papillary cystadenocarcinomatous pattern. X25.

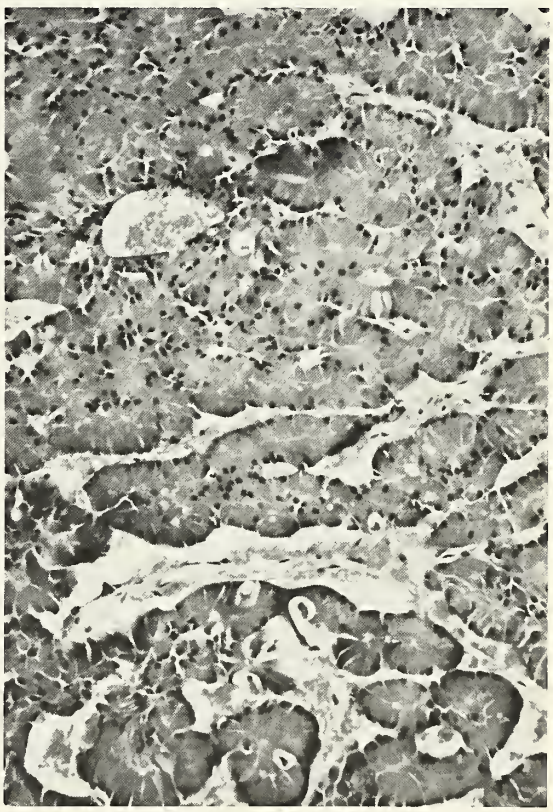


Figure 107
ADENOCARCINOMA
This neoplasm of the nasal septum has a definite acinic cell adenocarcinomatous micromorphology with a serous type cell element. X160.

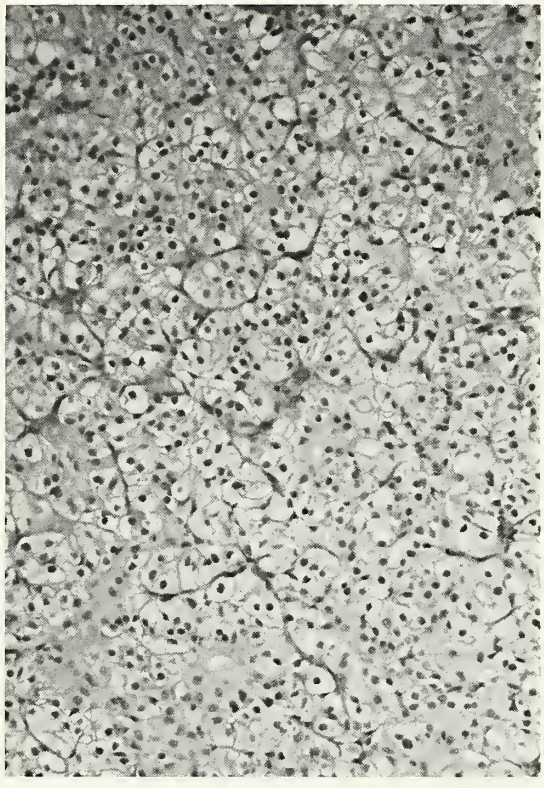


Figure 108
ADENOCARCINOMA
This nasal cavity neoplasm is a clear cell acinic cell adenocarcinoma and the similarity to a renal cell carcinoma is obvious, supporting the necessity of ruling out metastasis from a distant primary in practically all adenocarcinomas of the upper respiratory tract. X160.

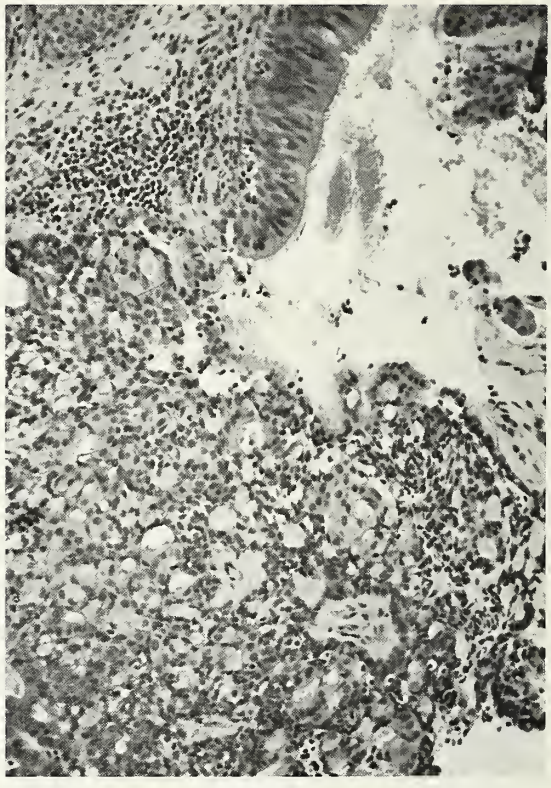
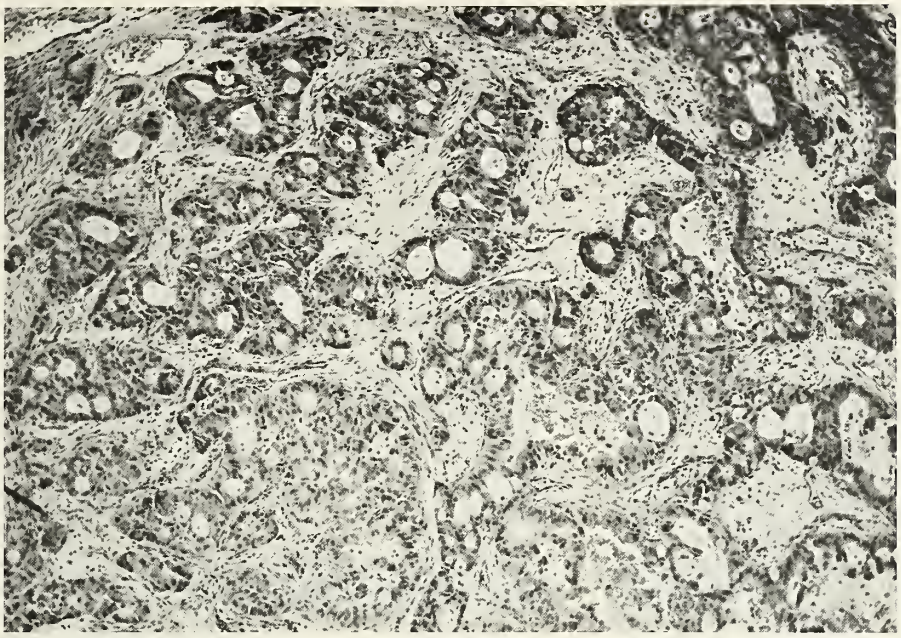


Figure 109
ADENOCARCINOMA
This micrograph supports the origin of a low-grade adenocarcinoma of the sinonasal tract from the respiratory mucosa, with a transition of the neoplasm from the adjacent ciliated respiratory mucosa. X160.

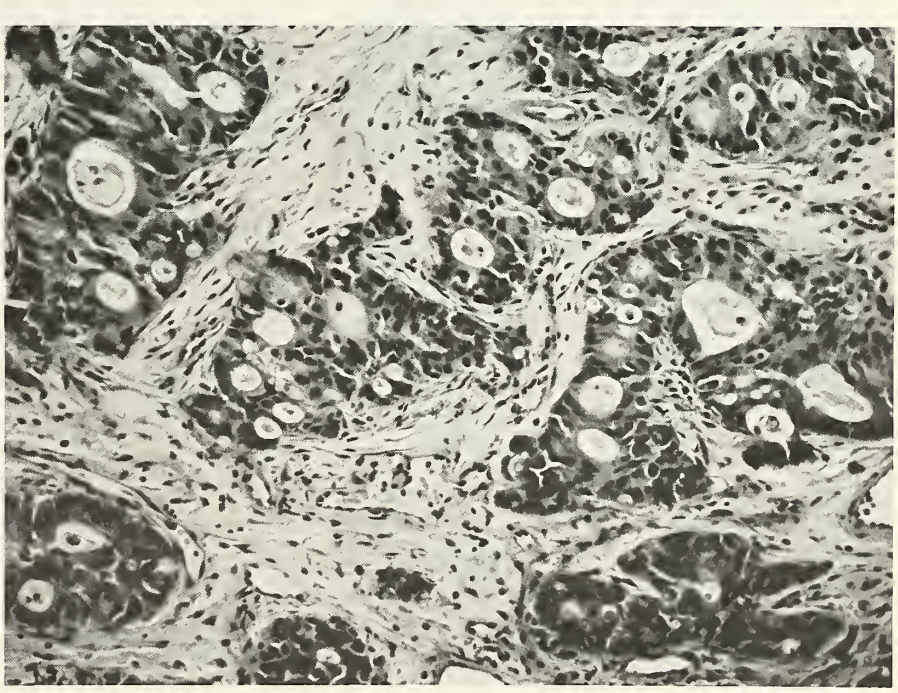
Hyams). The sessile adenocarcinoma covers a broader expanse of the surface, retains little similarity to the cells of origin, and manifests a poorer prognosis than does the papillary, noncolonic-like adenocarcinoma. The alveolar-mucoid variant may be polypoid or sessile and shares the poorer prognosis. Its appearance has been likened to the colloid carcinoma of the breast or colon (Batsakis et al., 1963). In a few cases of this latter type, Paneth-like cells have been found.

Natural History and Treatment. The overall biologic behavior of sinonasal tract adenocarcinoma is not unlike that of adenoid cystic carcinoma. Cervical lymph node metastases are variable. The study by Spiro and associates (1973) reports the highest incidence of any series, 28 percent. Distant metastases, however, are far less than those recorded for adenoid cystic carcinoma.

Local uncontrolled growth accounts for the death of the patient. Again, the five-year survival estimates are not adequate. Considerable attrition occurs when observation periods are extended to 10 and 15 years. Papillary adenocarcinoma has little tendency to metastasize and the survival rate of this type of adenocarcinoma exceeds that of the other subtypes.



A



B

Figure 110
ADENOCARCINOMA
(A) The histology of this lesion is that of a poorly differentiated or high-grade adenocarcinoma of the sinonasal tract. X63. (B) Higher magnification demonstrates the increased anaplasia. X160.

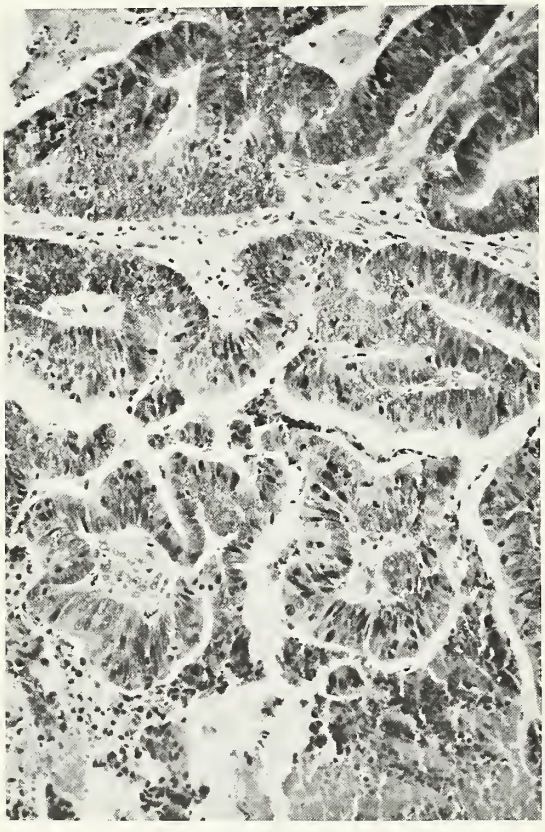


Figure 111
ADENOCARCINOMA
A high-grade papillary cystadenocarcinoma of the sinonasal tract emphasizes the "colonic" appearance. This is the microscopic pattern of the so-called woodworkers' carcinoma of the sinonasal tract. X63.

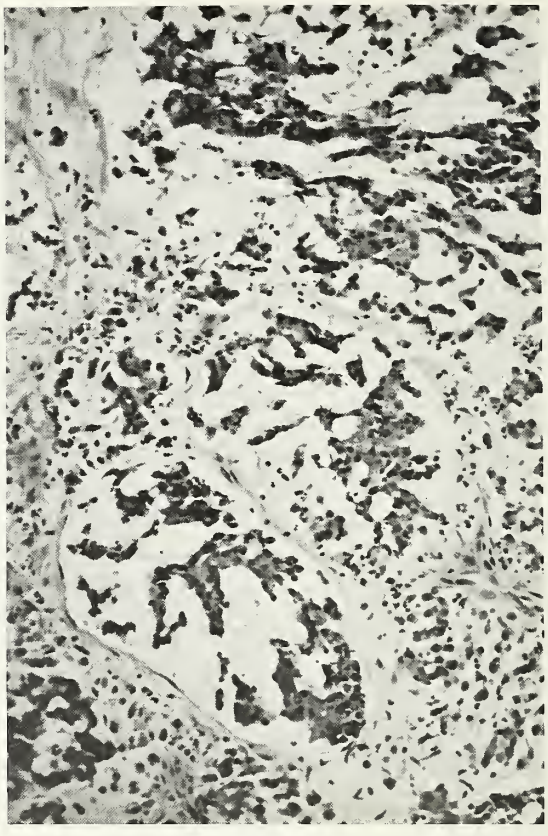


Figure 112
ADENOCARCINOMA
This colloid type high-grade adenocarcinoma of the sinonasal tract imitates a form of colonic-like adenocarcinoma. X160.

A series of adenocarcinomas of the sinonasal tract from the AFIP-OTR material (Heffner et al.) were classified histologically as low-grade (23 patients) and high-grade adenocarcinoma (27 patients). The low-grade adenocarcinomas with a median followup of 6.3 years had 2 of the 23 patients dying of their disease. There were 3 patients alive with disease and the remainder alive without disease. In high-grade adenocarcinomas, 21 patients were dead of their disease within three years of diagnosis. An additional 4 patients were alive with disease, while only 2 showed no evidence of residual tumor. In the series of Heffner and colleagues, the therapy was that of an essentially complete surgical removal with little benefit from irradiation or chemotherapy.

ADENOCARCINOMA, PHARYNX

The AFIP-OTR contained nine patients with adenocarcinoma of the pharynx (not further classified), all neoplasms arising in the nasopharynx. The ages ranged from 22 to 66 years, with the median of 44 years. There was a 2 to 1 female to male ratio. The symptoms, in order of decreasing frequency,

were nasal obstruction, mass, diplopia, and otitis media, with a symptom duration of two weeks to five months (average two months) prior to diagnosis. These nasopharyngeal neoplasms were essentially exophytic and localized, with only one patient revealing extension into surrounding vital cavities. This same patient was the only one with metastasis to cervical lymph nodes.

Histology. Eight of the nine patients revealed a papillary cystadenocarcinoma micromorphology composed of generally single-layered cuboidal or columnar epithelium with little significant anaplasia or mitotic activity. The microscopy did support a metastatic papillary carcinoma of the thyroid, but there was definite cellular mucin production and immunoperoxidase reaction against thyroglobulin was negative. One lesion that microscopically revealed a pure glandular architecture was the only one that was clinically locally aggressive with invasion into the adjacent intracranial space. Treatment was mainly surgical. Follow-up information revealed that five of the six patients with the exophytic papillary cystadenocarcinoma pattern showed no evidence of disease from 6 months to 11 years after surgical removal. One patient had a recurrence one year after removal. Histology of the one fatality showed the glandular pattern that extended to involve the cranial cavity and brain.

PITUITARY TYPE ADENOMA, NASOPHARYNX

As was noted in the histology of the nasopharynx, anterior pituitary-type cells can be found in the midline posterior superior area adjacent to Rathke's pouch. Therefore, pituitary-like neoplasms occur in the nasopharynx (figs. 23, 24). The AFIP-OTR material contains 7 cases, 3 of which presented the pituitary adenoma confined to the nasopharynx and 4 which revealed involvement of both the sphenoid sinus and nasopharynx. There was no sex predominance and ages at diagnosis extended from 24 to 81 years (median 41 years), with 5 patients being in the third to fifth decades. Symptoms were local destruction in 3 patients, meningitis in 2, and obstruction and endocrine abnormality in 1 case each. The histology was that of a chromophobe pituitary adenoma in 6 patients, and 1 patient revealed the micromorphology of an acidophilic adenoma. Followup was available in only 2 patients, with 1 being treated by surgical removal with no evidence of disease nine years following removal, and 1 treated with surgery and radiation with no evidence of disease three years later.

ADENOCARCINOMA, LARYNX

Table 7 reveals the experience of several medical centers with adenocarcinomatous neoplasms of the larynx. The AFIP-OTR data includes 26 patients with adenocarcinoma (not otherwise specified) diagnosed as primary laryngeal neoplasms. Twenty-two were male. The ages ranged from 19 to 75 years (median 59 years), with 23 patients 48 years or older. The prediagnostic symptoms varied from six weeks to two years (average four months). Symptoms, in order of decreasing frequency were hoarseness, dysphagia, pain, hemoptysis, and dyspnea. Only two lesions were subglottic, the remainder were described as arising from either the true vocal cord or the supraglottic areas. Gross appearance varied from a mucosa-covered small nodule to larger ulcerated masses that led to laryngeal distress. The histology was quite variable and confusing. The pattern of sheets of cells revealed occasional "cell rest"

Table 7

MUCOUS GLAND CARCINOMAS OF THE LARYNX

Series	Number of Laryngeal Cancers	Number of Mucous Gland Carcinomas	Histologic Types	Number
Mayo Clinic	3100	27	Adenocarcinoma	12
			Adenoid cystic	9
			Mucoepidermoid	6
Washington University	888	9	Adenocarcinoma	5
			Adenoid cystic	3
			Mucoepidermoid	1
Gustave-Roussy Institute	1342	5	Adenoid cystic	5
Memorial*	2793	20	Adenocarcinoma	13
			Adenoid cystic	3
			Mucoepidermoid	3
			Other	1
Padua University*	2052	21	Mucoepidermoid	10
			Adenocarcinoma	7
			Adenoid cystic	1
			Other	3

*Includes laryngopharynx

patterns leading to the consideration of a diagnosis of paraganglioma (figs. 113-115). Microscopic search most often revealed a typical glandular arrangement, and occasionally a papillary cystadenomatous architecture (fig. 106). The tumor cell was moderately well differentiated, cuboidal or columnar, without cilia, and with rare mitotic activity. Positive mucin staining was possible, but was usually scant. Paladugu and associates demonstrated immunoreactivity against calcitonin, somatastatin, and ACTH. Electron microscopy and special histochemical studies have demonstrated neurosecretory cytoplasmic granules (figs. 116, 117), leading to the suggestion that these laryngeal neoplasms are essentially a carcinoid tumor although no hormonal activity has been described (Paladugu et al.; Gapany-Gapanavicius and Kenan).

Treatment and Prognosis. Four of 6 patients, after local surgical removal, had no evidence of disease at two to eight years, 2 had recurrence at one and five years, with the latter patient also revealing pulmonary metastases at eight years. In 6 patients treated by partial laryngectomy, 3 had no disease in a two-year followup and 3 had metastases at two to three years, 1 dying of the disease. Four patients underwent laryngectomy and 3 were alive without disease for three to six years. The remaining patient died of other disease. Two patients were treated with only radiation; 1 died of disease at six months while the other had a recurrence at two years and died with disease at three years. Assured complete surgical removal would seem indicated in primary adenocarcinoma of the larynx.

A giant cell carcinoma of the larynx is discussed by Ribari and associates. This tumor is composed of numerous pleomorphic, multinucleated giant cells, often with starry

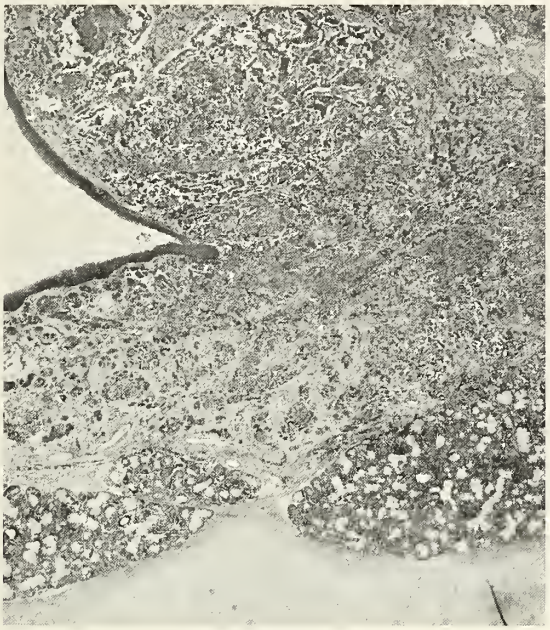


Figure 113
(Figures 113 and 114 are from the same patient)
ADENOCARCINOMA
A scanning view of a primary adenocarcinoma of the larynx in a 49 year old man. X25.

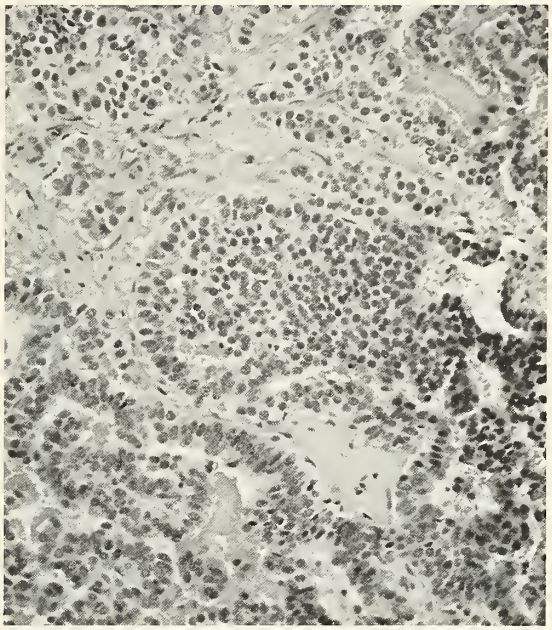


Figure 114
ADENOCARCINOMA
Note the essentially uniform neoplastic cellular element along with an area of sheetlike, proliferating, back-to-back gland arrangement. X160.

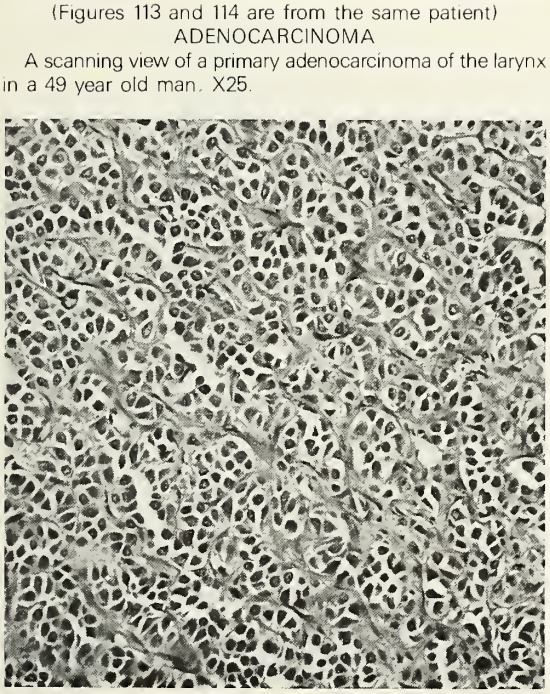


Figure 115
ADENOCARCINOMA
This pattern, seen in an occasional adenocarcinoma of the larynx, has led to the erroneous diagnosis of malignant paraganglioma. X160.

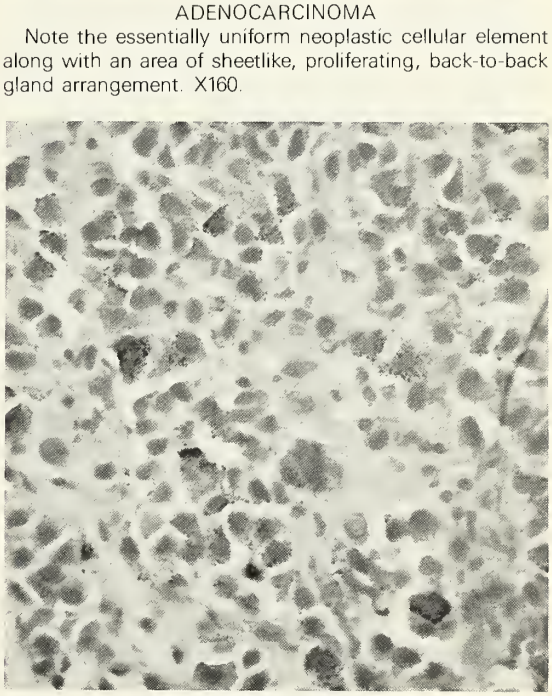


Figure 116
ADENOCARCINOMA
A Grimelius histochemical stain reveals the argyrophilic positivity in the neoplastic cells, indicative of the inclusion of neurosecretory granules. X400.

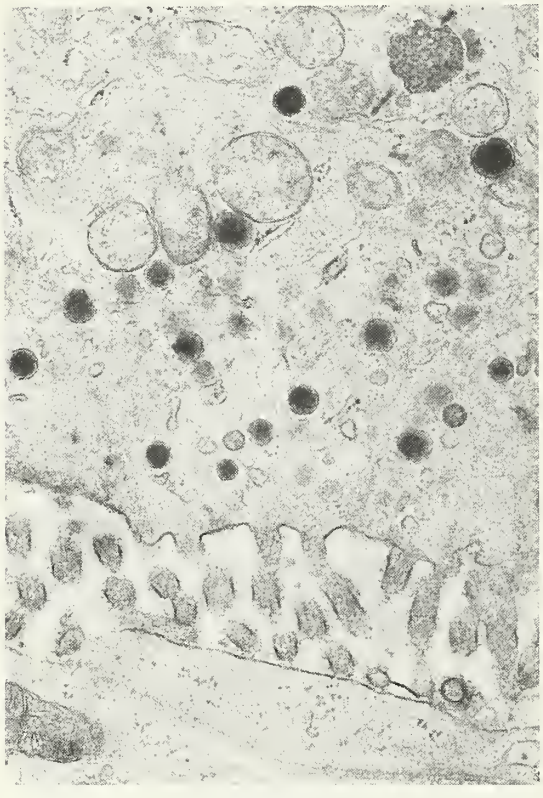


Figure 117
ADENOCARCINOMA
Electron microscopic view of an adenocarcinoma of the larynx reveals neurosecretory-like granules with electron-dense cores surrounded by a unit membrane. X30,000. (Fig. 5 from Paladugu, R.R., Nathwani, B.N., Goodstein, J., Dirdi, L.E., Memoli, V.E., and Gould, V.E. Carcinoma of the larynx with mucosubstance production and neuroendocrine differentiation. Cancer 49:343-349, 1982.)

acidophilic and vacuolated cytoplasm, supported by a delicate fibrovascular stroma. The tumor cells may resemble pleomorphic sarcomatous giant cells. Numerous atypical mitoses can be found. The cells may be isolated, in clusters, or around alveolar-like spaces. PAS positive granules are present in the cytoplasm of some cells, and some cells appear phagocytic. Necrosis and hemorrhage are inconspicuous. The relationship of giant cell adenocarcinoma to other malignant giant cell tumors of the larynx is unclear.

MUCOEPIDERMOID CARCINOMA, UPPER RESPIRATORY TRACT

SYNONYMS AND RELATED TERMS: Adenosquamous carcinoma; mucoepidermoid tumor.

Definition. Mucoepidermoid carcinoma is a malignant epithelial neoplasm characterized by the presence of squamous cells, mucus-secreting cells, and cells of intermediate type. In evaluating the mucoepidermoid carcinoma of the upper respiratory tract contained in AFIP-OTR material, there is histologic support for considering this entity as arising from the mucosa rather than from the mucoserous glands.

There were 11 patients recorded in AFIP-OTR who were diagnosed as having mucoepidermoid carcinoma of the sinonasal tract. Ages were from 14 to 80 years (median 40 years), with no sex preference. Half arose from the nasal cavity, both lateral wall and septum, and the remainder from the confines of the maxillary sinus. In the nasal cavity, obstruction and epistaxis were the symptoms, while in the sinuses, headache, fistula, and mass were the presenting signs. Follow-up information was obtained in four patients. Two patients, one with nasal cavity origin and the other with maxillary sinus neoplasm origin, were tumor free four years following surgical removal. The two remaining patients, with neoplasm arising in the nasal cavity, were treated with irradiation therapy only and were alive and well at a 2- and 16-year followup.

Nine patients with primary mucoepidermoid carcinoma in the pharynx ranged in age from 33 to 69 years (median 54 years), with no sex predominance. All neoplasms arose from the nasopharynx and produced mainly pain, otitis media, and epistaxis, with an average symptom duration of six months prior to diagnosis. Follow-up

information on two patients revealed that one was treated by irradiation therapy and died of the disease in one year post diagnosis, and the other, treated by local surgery and radiation, was alive with residual disease at two years.

There were 21 patients with diagnosed mucoepidermoid carcinoma of the larynx in the AFIP-OTR data (Damiani et al.). Ages ranged from 25 to 76 years (median 57 years), with a male to female ratio of 6 to 1. Presenting signs and symptoms were identical to those of squamous cell carcinoma of the larynx, such as hoarseness, hemoptysis, foreign body sensation, dysphagia, and neck mass. The average symptom duration prior to diagnosis was 9.3 months. Seven of the patients presented palpable cervical lymphadenopathy at original diagnosis. The laryngeal mucoepidermoid carcinomas arose supraglottically in 15 patients and glottically in 6. The neoplasms measured from .6 cm to 5 cm in diameter.

Gross. The gross appearance (fig. 118) is indistinguishable from the usual fungating squamous cell carcinoma of the larynx.

Microscopic. The AFIP-OTR material supports both clinically and histologically the idea of origin of mucoepidermoid carcinoma of the upper respiratory tract from the respiratory mucosa (fig. 119). There is a definite squamous element varying from a nonkeratinizing, transitional, epithelial pattern to a prominent keratinizing category. Mucus-positive glands and individual cells vary in quantity and differentiation. The cytologic hallmark of the salivary gland mucoepidermoid carcinoma: the intimate association of

Figure 118
MUCOEPIDERMOID CARCINOMA
This mucoepidermoid carcinoma involved the right true vocal cord and ventricular folds.

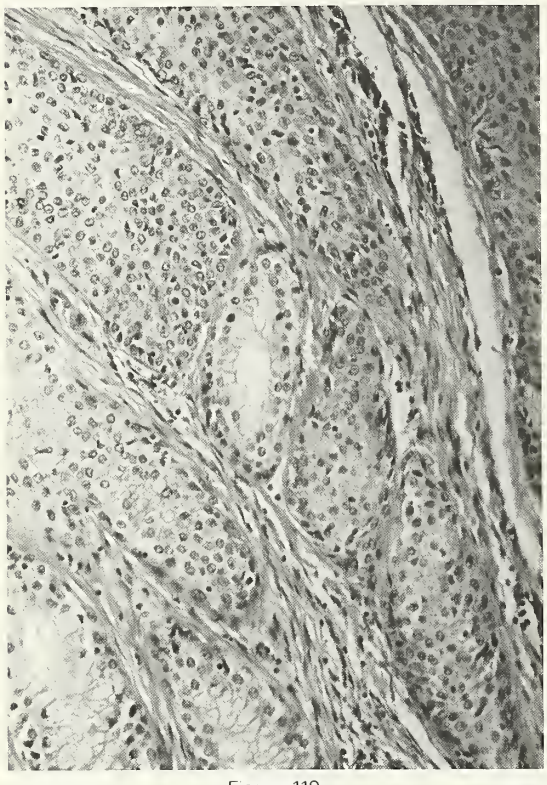


Figure 119
MUCOEPIDERMOID CARCINOMA
This illustration emphasizes the so-called intermediate type squamous cell. X160.

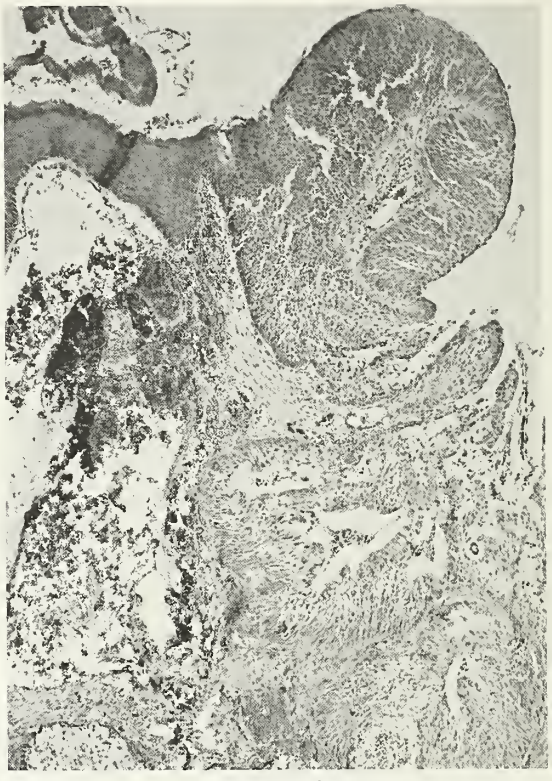


Figure 120
MUCOEPIDERMOID CARCINOMA
Biopsy of a fungating lesion of the supraglottic laryngeal area showed a neoplasm arising from the mucosa, with microscopic characteristics of a mucoepidermoid carcinoma. X63.

epidermoid and mucous cells appears less emphasized. There also seems to be an increased keratinization of the epidermoid portion of the upper respiratory tract mucoepidermoid carcinomas when compared with the salivary gland type mucoepidermoid carcinoma. Perhaps mucoepidermoid carcinoma of the upper respiratory tract essentially represents squamous cell carcinoma arising from the respiratory mucosa in which the neoplastic mucosal cell retains in part its ability to form a mucous cell neoplastic proliferation. This possibility has supported the suggestion that these neoplasms might be better termed "adenosquamous carcinoma" (Damiani et al.).

For prognostic and treatment planning it is well to histologically classify these upper respiratory tract mucoepidermoid carcinomas into low-grade (well differentiated) and high-grade (poorly differentiated). The former will show well formed glandular spaces lined with uniform mucous cells alternating with areas of nonanaplastic epidermoid cells (fig. 120). The high-grade neoplasm will reveal a more undifferentiated squamous component forming the major part of the neoplasm together with, most likely, a poorly formed mucus element. Ferlito describes a form of upper respiratory tract mucoepidermoid carcinoma noted by the presence of large, solid masses composed of "glassy" cells bounded by

fibrous tissue. Their cytoplasm is clear and PAS-negative.

Therapy and Prognosis. The therapy for mucoepidermoid carcinoma of the upper respiratory tract is essentially that which would be expected for squamous cell carcinoma of the same anatomic area. Assured complete surgical removal is the general aim; however, in isolated incidences radiation therapy has proved curative. In the 21 patients with laryngeal mucoepidermoid carcinomas contained in the AFIP-OTR material (Damiani et al.), the 8 patients with well differentiated low-grade neoplasm all survived over five years following treatment, while the remaining patients with high-grade, poorly differentiated, laryngeal mucoepidermoid carcinoma, regardless of therapeutic modality, had only a 50 percent survival in three years.

ACINIC CELL CARCINOMA, CLEAR CELL CARCINOMA, AND ANAPLASTIC CARCINOMA OF THE UPPER RESPIRATORY TRACT

Acinic cell carcinoma and clear cell carcinoma, when they occur in the upper respiratory tract, arise from mucoserous glands. They represent no more than 0.5 to 1.0 percent of all mucoserous gland tumors of the anatomic area (Perzin et al., 1981). Acinic cell carcinoma is characterized by acini lined by cells resembling those of the serous cells of the mucoserous glands (fig. 121). Clear cell carcinoma is composed of relatively large cells with a clear cytoplasm which is negative for mucin stains. They may or may not contain glycogen and may be papillary. Both tumors are locally infiltrative and, very likely, their biologic behavior is akin to intermediate grade mucoepidermoid carcinoma (Batsakis and Regezi). In the series of adenocarcinomas of the sinonasal tract studied by Heffner and associates, these acinic cell and clear cell carcinomas would have been included under the classification of low-grade adenocarcinoma. It is noted here that "clear cells" may be present in varying degrees in other salivary gland neoplasms, particularly acinic cell carcinomas, mucoepidermoid carcinomas, and oncocytic tumors. Such cells are largely due to artifacts in the processing of tissue.

Undifferentiated adenocarcinomas or anaplastic forms of adenocarcinoma of the upper

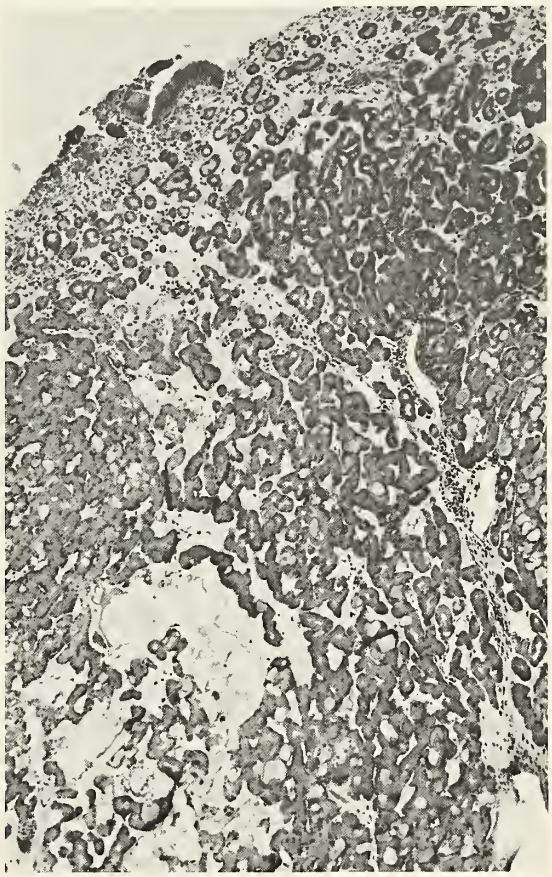


Figure 121
ACINIC CELL ADENOCARCINOMA
This acinic cell adenocarcinoma, arising in the nasal septum, shows mainly a serous type glandular arrangement with a rare clear or mucous cell. X63.

respiratory tract are distinctly uncommon. Koss and colleagues reported 14 examples of anaplastic, small cell carcinoma of the mucoserous glands and minor salivary glands and remarked on their histologic similarity to oat cell carcinoma of the bronchus. Five of the lesions were in the upper respiratory airway (nasal cavity, paranasal sinuses, and epiglottis). The remainder were oral lesions. All the neoplasms were located beneath histologically normal surface epithelium whenever it was not ulcerated. Remnants of mucoserous salivary glands were identifiable in every one of the primary tumors.

The neoplasms are composed of elongated small cells with very scant cytoplasm and intensely hyperchromatic nuclei. The cells may be arrayed in sheets, in some instances having the general configuration of ducts. In other instances, the cells infiltrate the stroma in a haphazard manner. Necrosis in the neoplasms is common. A hyaline stroma surrounding tumor cells may be prominent. The cellular presentation is most often a monotonous one. Koss and associates observed spindle and giant cell forms in one case and keratinization in another.

The anaplastic carcinomas have frequent cervical lymph node metastases (50 percent of Koss and associates' series). Four of the 14 patients studied by Koss and associates survived five years or longer.

ADENOCARCINOMA METASTATIC TO UPPER RESPIRATORY TRACT FROM REGIONAL AND DISTAL SITES

In the diagnosis of adenocarcinoma of the upper respiratory tract, the possibility of metastasis from a regional or distal primary site must always be considered. Metastasis to the sinonasal tract infrequently develops from primary tumors which occur below the clavicles (Table 8). However, there is complete unanimity concerning the type of neo-

Table 8

METASTATIC FOCI TO THE PARANASAL SINUSES

Primary Tumor	Maxilla	Ethmoid	Frontal	Sphenoid	Nose	Nasopharynx	Palate	Alveolar Ridge
Kidney	19	13	9	2	6	2	1	1
Bronchus	3	1	1	1	2	1		4
Breast	7				1			
Urogenital ridge	5		1				1	2
GI tract	2			2				1
Miscellaneous								
Thyroid			1	1	1			
Pancreas	1	1			1			
Melanoma of skin	1				1			
Adrenal	2							
Total	40	15	12	6	12	3	2	8

Adapted from Bernstein, J.M., Montgomery, W.W., and Balogh, K., Jr. Metastatic tumors to the maxilla, nose, and paranasal sinuses. Laryngscope 76:621-650, 1966.

Table 9

METASTATIC NEOPLASIA OF LARYNX FROM DISTANT PRIMARIES

Primary Site and/or Neoplastic Classification	No. Cases
Renal adenocarcinoma (hypernephroma)	7
Breast carcinoma	4
Lung carcinoma	4
Gastrointestinal tract carcinoma	3
Prostatic adenocarcinoma	2
Melanoma	15
Miscellaneous neoplasia and sites	3

Adapted from Whicker, J.H., Carder, G.A., and Devine, K.D. Metastasis to the larynx. Arch. Otolaryngol. 96:182-184, 1972.

plasm most often encountered in these instances — the renal cell carcinoma (Batsakis and McBurney). The second most frequently occurring metastases are those from lung and breast. Considerably less frequent sites of primaries are the gastrointestinal and urogenital tracts.

The average age of patients with metastatic renal cell carcinoma in the sinonasal tract is more than 65 years. This average is similar to patients with metastatic breast carcinoma to the sinonasal tract and 10 years higher than those with metastases from bronchogenic and gastrointestinal neoplasms.

The clinical manifestations of metastases to the sinonasal tract usually are nonspecific, with swelling, pain, or nasal obstruction. Metastatic renal cell carcinoma has a significant tendency to cause epistaxis. Signs and symptoms referable to nasal or sinus disease often precede discovery of the primary neoplasm, and this is especially true with metastatic renal cell carcinoma.

Prognosis for patients with metastatic carcinoma of the nose and paranasal sinuses is, in general, the same as that for patients with generalized carcinomatosis. Possible exceptions are those cases in which the lesion of the sinonasal tract is the only metastatic focus. This is particularly true in the case of metastatic renal cell carcinoma. Removal of the metastasis and the tumor may show a good end result (Batsakis and McBurney).

The larynx is a rare site of metastasis from regional or distal sites (Table 9). Metastatic renal cell carcinoma has been the most frequent offender, followed by melanoma and primaries in breast, lung, prostate gland, and gastrointestinal tract.

NECROTIZING SIALOMETAPLASIA

The benign, self-limited, and reparative lesion, necrotizing sialometaplasia, must be considered in the evaluation of epithelial (squamous or glandular) malignancy in the sinonasal tract. The lesion may occur in any salivary tissue, but has been most often reported in the palate, where it arises spontaneously and from unknown causes, although the pathophysiology supports a temporary compromise of the blood supply to the anatomic area affected. In the oral cavity, sinonasal tract, larynx, and major salivary glands the lesion nearly always follows local tissue injury, e.g., after surgery or instrumentation like endoscopy (Maisel et al.).

Two processes are characteristic of the histologic appearance: necrosis of salivary or mucoserous gland tissue, and a squamous metaplastic cell proliferation which replaces some of the acini as they become depleted of their original cells (Abrams et al.) (figs. 122, 123). The processes are reflected to varying degrees within the confines of the salivary gland lobule with a preservation of the overall lobular architecture.

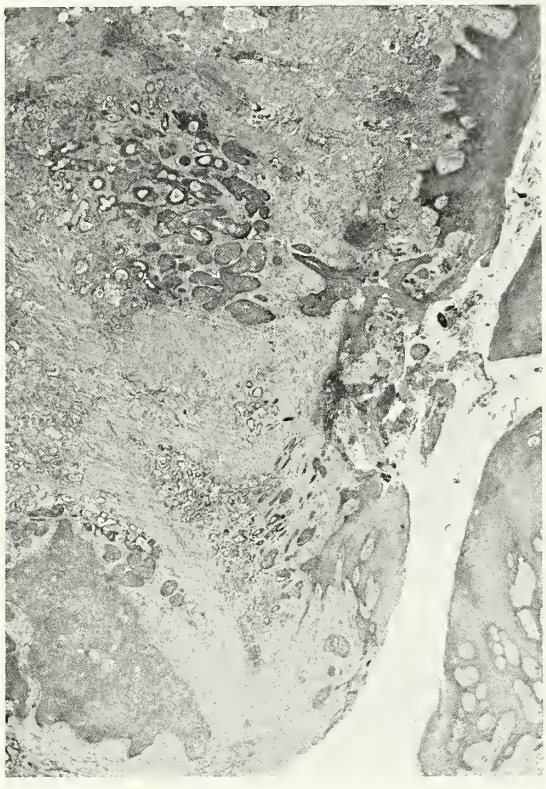


Figure 122
NECROTIZING SIALADENITIS
(SIALOMETAPLASIA?)
A scanning microscopic view of an ulcerative lesion of the oral surface of the hard palate with ulceration of the surface and squamous metaplastic change of the lobules of the minor salivary glands. X25.

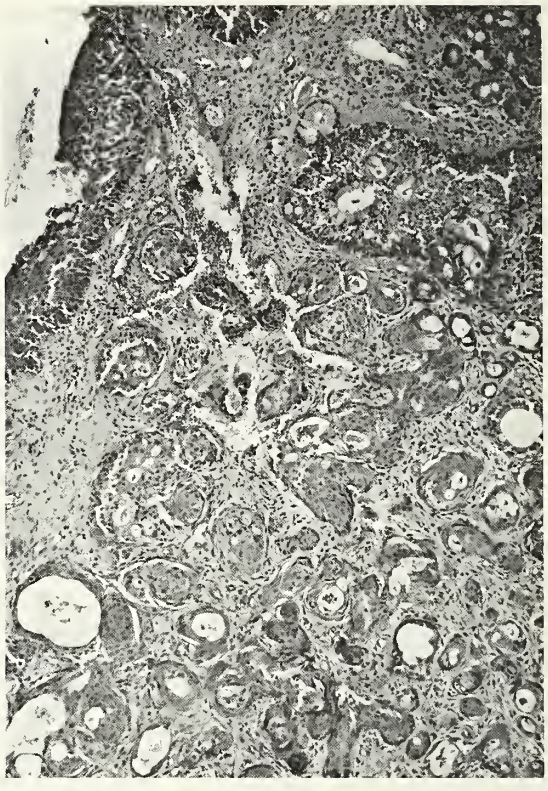


Figure 123
NECROTIZING SIALADENITIS
(SIALOMETAPLASIA?)
A biopsy of an ulcerated area of the nasal turbinates showed squamous metaplastic involvement of the mucoserous glands, suggesting a diagnosis of mucoepidermoid carcinoma. X160.

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MESENCHYMAL TUMORS

FIBROMA

Pure benign neoplasms of the fibrocyte are rare in any part of the body and there is some doubt whether such an entity exists. "Fibroma" has been incorrectly applied, but without danger, to certain pedunculated lesions of the skin which are either malformations or, more likely, hyperplastic proliferations secondary to some form of injury. The small absence of hazard cannot be held for deeper soft tissue tumors where a histologic diagnosis of "fibroma" is suspect. In these locations, such lesions represent reactive processes or a tumefaction that would fit in the classification of the fibromatoses.

Suspicion should also be attached to a diagnosis of "fibroma" given to a supporting tissue tumor of the upper respiratory tract and hypopharynx. They have been recorded in the nasal cavity, pharynx, and larynx (Fu and Perzin, 1976). In the nasal cavity and elsewhere in the upper respiratory tract, such lesions usually are polypoid and composed of mature fibrous tissue and probably represent a reactive process rather than a true neoplasm of fibroblasts.

Nodular fasciitis (figs. 124, 125), which is considered most likely a reactive process,

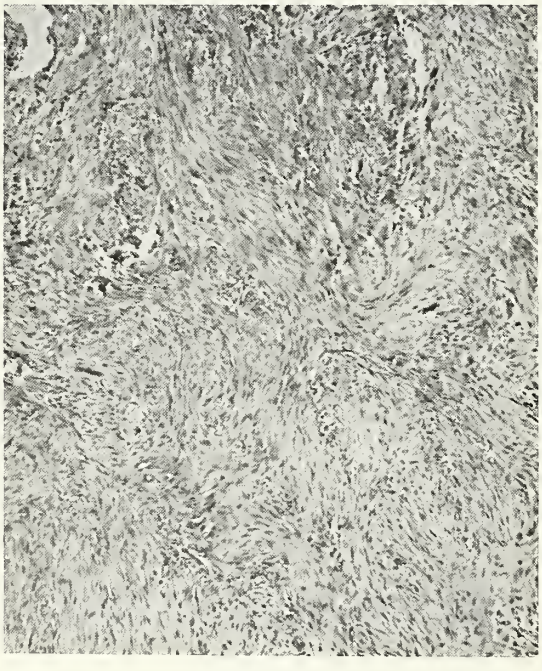

Figure 124
NODULAR FASCIITIS
A nodular fasciitis, involving the periparotid gland area, with the storiform architecture of the bipolar spindle fibroblastic cells. X63.

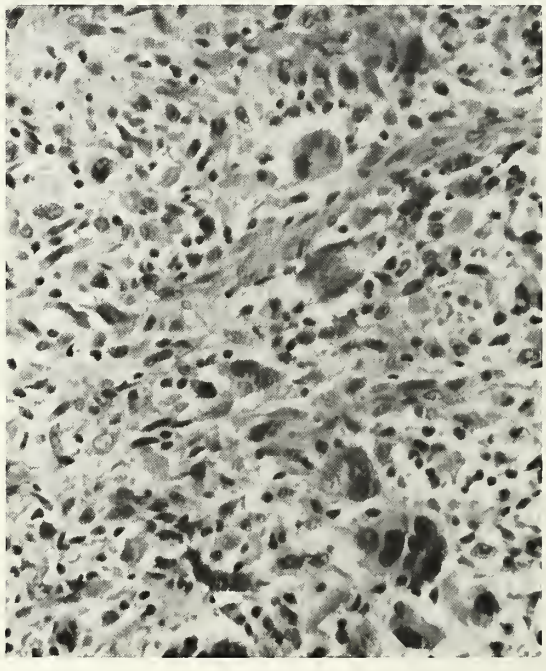

Figure 125
NODULAR FASCIITIS
This nodular fasciitis exhibits a fibromatous appearance, with multiple nucleated giant cells. X160.

does frequently involve the soft tissues of the neck (Dahl and Jarlstedt) and, rarely, the oral and perioral tissues, but there is dispute as to whether it does occur in the soft tissue of the upper respiratory tract. The reader is referred to the Fascicle on Tumors of the Soft Tissues for a comprehensive discussion of nodular fasciitis.

FIBROMATOSIS

Definition. A fibromatosis may be defined as an infiltrating fibroblastic proliferation showing none of the histologic features of an inflammatory response nor features of unequivocal neoplasia (Mackenzie). These lesions may occur anywhere and to any extent. They may be fatal or occasion, or be relatively harmless. They are encountered from fetal life to old age.

While the lesions exhibit differences in biologic behavior when found in different parts of the body, they share common features. Muscle and fibroadipose tissue are replaced by, or infiltrated with, fibrous tissue of varying cellularity. The lesions may be single, diffuse, or multifocal. The fibroblasts are well differentiated, uniform in size, and often devoid of mitotic activity. They may mimic fibrosarcoma by their infiltrative capacity and recurrences, but do not metastasize. Terms used as synonyms, such as nonmetastasizing fibrosarcoma or fibrosarcoma grade I (desmoid type), are undesirable, since the suffix sarcoma, we believe, should be reserved for those supporting tissue tumors capable of generating metastases (Mackenzie).

Types. There are different types of fibromatosis described which are classified essentially on their anatomic location, the age group of involvement, or relationship to a hereditary or congenital factor. This discussion will center collectively on the entity fibromatosis as an unusual tumor of the nasal cavity, paranasal sinus, and larynx, and the secondary invasion of these structures by aggressive behavior of the fibromatosis that could arise in the adjacent soft tissue. In the head and neck, fibromatosis may be particularly difficult to eradicate surgically because of the anatomy of the area involved (Conley et al., 1966; Allen). The term "aggressive" fibromatosis is more in line with the overall behavior of the entity. The AFIP-OTR listed 37 patients with fibromatosis in the sinonasal tract, ranging from 5 to 76 years of age, with the third and fourth decades the most common. There was no sex preference. In the AFIP-OTR material, 13 patients revealed involvement only of the maxillary antrum, 11 showed nasal cavity origin, and 13 revealed involvement of both nasal cavity and sinus (maxillary antrum).

Fu and Perzin (1976) have described six patients with fibromatosis of the nasal cavity and paranasal sinuses. These were located primarily in the nasal turbinates and maxillary sinuses. Their gross presentation is not unlike that of fibromatoses elsewhere in the body — firm, white, fibrous masses that infiltrate adjacent tissues. Those tumors involving the maxillary sinus partially or completely fill the sinus cavity.

The biologic behavior of these fibromatoses also follows that of their extrasinonasal counterparts, in that recurrences are common and death may be due to lack of local control of the lesion.

Fu and Perzin (1976) also describe a patient with multicentric fibromatosis with paranasal sinus involvement.

Fibromatosis in the larynx is definitely unusual and presents almost exclusively in infants and children. The laryngeal lesion may be an isolated one or be a component of congenital generalized fibromatosis. The local-

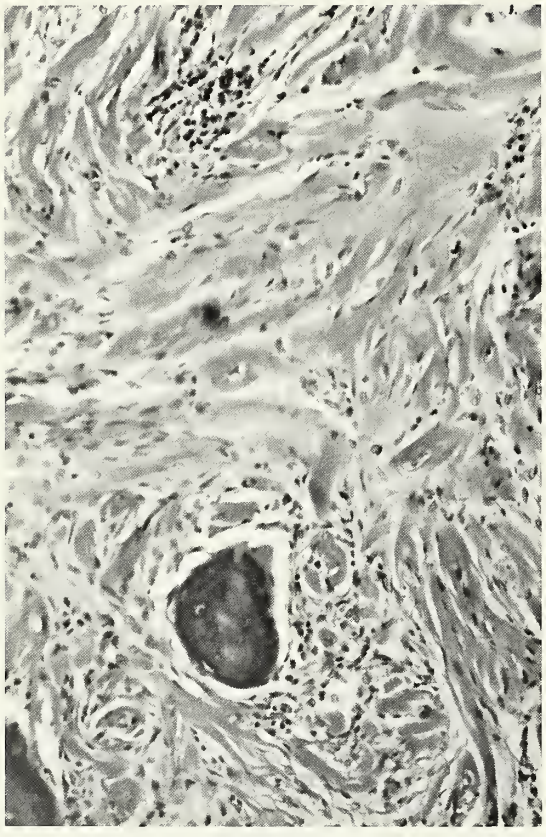

Figure 126
FIBROMATOSIS
Note the bland histology of the locally destructive fibrous tissue proliferation in this aggressive fibromatosis of the maxillary sinus of an adult. X160.

ized form appears sporadically and without a recognized antecedent event. In common with other fibromatoses, there is a propensity for recurrence and local invasiveness.

Microscopic. The typical fibromatosis is composed of relatively mature fibrous tissue with an abundant collagenous stroma (fig. 126). The spindle-shaped cells demonstrate little or no pleomorphism or hyperchromatism and are usually arranged in bundles. Mitoses are rare. Adjacent tissue is involved.

Differential Diagnosis. In the head and neck area, the microscopic differential diagnosis consists of fibrosarcoma, fibro-osseous lesions such as ossifying fibroma and cementifying fibroma, myxoma, neurofibroma, and angiofibroma. Occasionally, prominent vascularity in a fibromatosis may cause confusion. The angiofibroma should have stellate-shaped stromal cells, which do not grow in bundles as do the cells of a fibromatosis. In general, also, fibrous tissue tumor should not have the large, irregular, vascular channels seen in angiofibroma.

FIBROSARCOMA

In the head and neck, fibrosarcoma (excluding the neurogenous sarcomas) is uncommon. Formerly, many spindle cell sarcomas of other classifications (i.e., malignant fibrohistiocytomas) were indiscriminately classified as fibrosarcoma.

Definition. The fibrosarcoma is a malignant circumscribed or infiltrating tumor composed predominantly of a spindle-shaped cell which produces reticulin and collagen and shows no evidence of other forms of cellular differentiation.

The following statement by Fu and Perzin (1976) should be routinely applied in the evaluation of the diagnosis of a potential fibrosarcoma of the head and neck. They state: "the diagnosis of fibrosarcoma is made histologically when other tumors which may demonstrate fibrous tissue and collagen have been ruled out . . . only after examining multiple sections and special stains may the pathologist rule out these other lesions."

Nasal and Paranasal Fibrosarcoma

Gross. In the nasal and paranasal sinus region, fibrosarcomas may be polypoid or sessile lesions. They are not encapsulated and destruction of the adjacent bone is common. The cut surface of the tumors

generally manifest a homogenous, firm, white appearance.

Microscopic. The tumors are highly cellular and composed of elongated, spindle-shaped cells arranged in bundles (figs. 127, 128). A "herringbone" pattern may often be present.

Both cells and nuclei are relatively uniform. The nuclei usually do not demonstrate a great deal of pleomorphism. A moderate to marked mitotic activity, in contrast to the fibromatosis, may be seen. The degree of cellularity, number of mitoses, and amount of collagen often is variable even within a given tumor. Collagen production is favored in the less cellular zones. A prominent vascular pattern may be focally present. When occurring in the sinonasal tract, the majority of fibrosarcomas are comparatively well differentiated.

Differential Diagnosis. Lesions that must be excluded are: the fibromatoses; some osteogenic sarcomas and rhabdomyosarcomas; leiomyosarcomas; synovial sarcoma; hemangiopericytoma; neurogenous neoplasms; spindle cell carcinoma; and reactive fibrous processes.

Natural History and Treatment. Fu and Perzin (1976) found 7 well documented cases of fibrosarcoma of the nasal cavity, paranasal

Figure 127
(Figures 127 and 128 are from the same patient)
FIBROSARCOMA
This well differentiated fibrosarcoma of the sinonasal tract has a fascicular cellular arrangement of bipolar spindle cells, suggesting a "herringbone" pattern. X63.

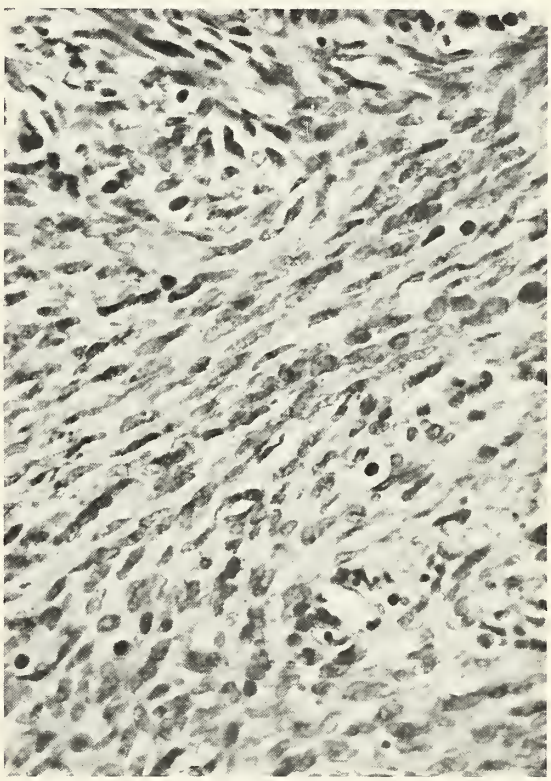

Figure 128
FIBROSARCOMA
Higher magnification of the previous illustration depicts the cellularity confirming a low-grade fibrosarcomatous proliferation. X160.

sinuses, and nasopharynx in the literature and added 13 patients of their own. The AFIP-OTR material contains 70 cases diagnosed as fibrosarcoma of the sinonasal tract, most being of low-grade histology and the majority arising in the nasal cavity. The ages of patients were mainly in the sixth and seventh decades, with a rare young adult or pediatric patient included. There was a moderate female predominance. Fu and Perzin concluded that treatment, if possible, should be large block resection. Limited local and inadequate excisions are usually associated with recurrences. Survival of patients is related to grade of differentiation of the tumor and local extent at the time of surgical excision (Swain et al.).

Some patients with well differentiated fibrosarcoma, who are listed in the AFIP-OTR, did not experience a recurrence until six years following original surgical removal. Fibrosarcomas have been identified as arising in the temporal bone area and some have been associated with previous radiation therapy to the area, particularly as treatment for pituitary neoplasms. Death is due to uncontrolled local disease. Metastases are unusual and are associated with the rare poorly differentiated fibrosarcoma (fig. 129).

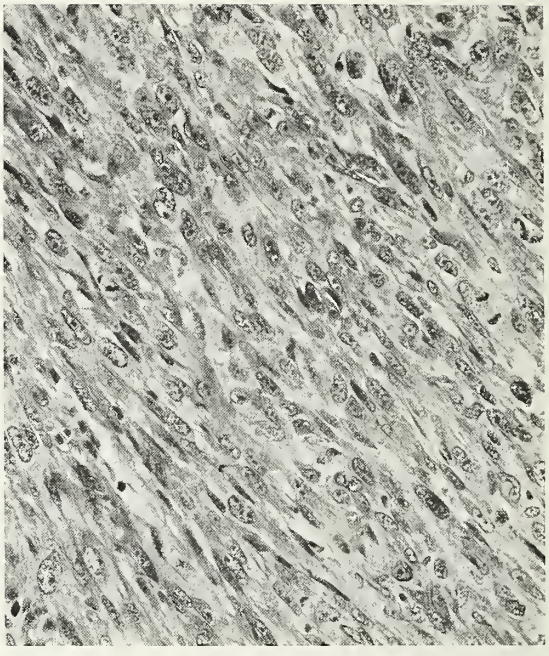

Figure 129
FIBROSARCOMA
This fibrosarcoma of the sinonasal tract exhibited clinically prominent local aggression along with metastatic disease. The histology supports a more undifferentiated fibrosarcoma. X160.

Fibrosarcoma of the Larynx

Incidence. By 1969, 32 pathologically proven and acceptable cases of laryngeal fibrosarcoma had been reported (Batsakis and Fox). Approximately 70 percent of the patients were over the age of 50 years at the time of initial diagnosis, and males dominated with a ratio of 4 to 1.

Gross. Most of the fibrosarcomas arose from the anterior cords or commissure, or both; others were found at the level of the cricoid cartilage or ventricle. Only a few presented as fungating or ulcerating masses; the majority had a nodular or pedunculated configuration.

Spread. In the larynx, there is a marked contrast in the prognosis, depending upon whether the neoplasm is well or poorly differentiated (Batsakis and Fox). Regardless of differentiation, the laryngeal fibrosarcoma rarely metastasizes. Laryngeal fibrosarcomas spread along blood vessels, most often by infiltration along the fascial planes or muscle in the environs of the larynx. Nearly all patients with poorly differentiated fibrosarcomas of the larynx die within three years of operation.

Differential Diagnosis. The important microscopic differential diagnostic problem is the spindle cell carcinoma of the larynx (see section on Spindle Cell Carcinoma).

LIPOMA

Despite the fact that lipoblastic tumors (figs. 130-132) are very likely the most common of all supporting tissue lesions, they are infrequent in the head and neck and rarely intrinsic to the upper airway.

Lipomas of the pharyngeal region may be striking clinical entities. Their site of origin can be practically any area: pharyngoepiglottic; aryepiglottic or glossoepiglottic folds; valleculae; rarely, the choanal edge; palatopharyngeal fold or lateral hypopharynx; the vault of the nasopharynx; region of the torus tubarius; or the soft palate. The greatest number originate in the hypopharynx. The lower pole of the tonsil, aryepiglottic fold, and wall of the hypopharynx are the main areas of attachment for the hypopharyngeal lipoma. Nearly a quarter of patients present with more than one synchronous lipoma. Respiratory symptoms are dependent upon the position of the lipomas. Two of the 24 patients reviewed by Mansson and associates died by suffocation.

Hibernoma (fig. 132) is a rare benign tumor of brown fat that has not been recorded in the upper respiratory tract but apparently can occur in the soft tissue of the neck. According to Rigor and associates, a malignant potential of the tumor has not been proved. It has favored the female and the third decade.

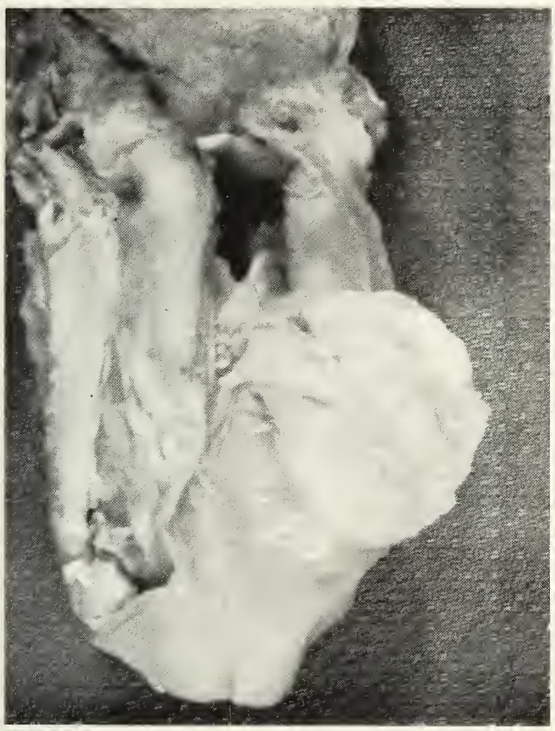

Figure 130
LIPOMA
An elderly woman died of apparent acute airway obstruction. At autopsy it was found that this lipoma, arising from the posterior surface of the cricoid, caused obstruction of the laryngeal inlet.

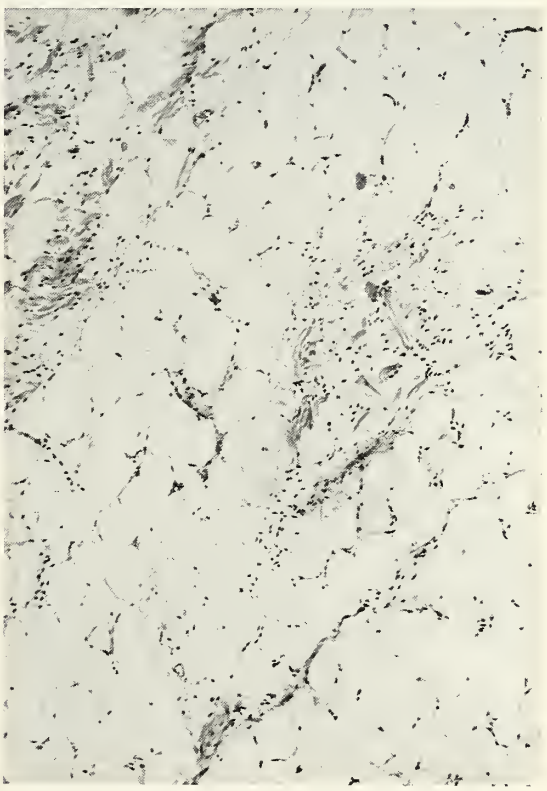

Figure 131
LIPOMA
A lipoma of the pharyngeal area contains benign fatty tissue. X63.

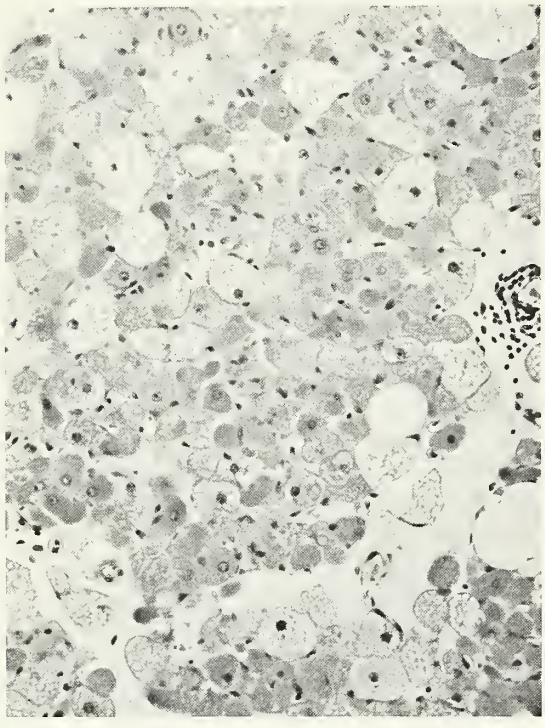

Figure 132
HIBERNOMA
A hibernoma arising in the soft tissue of the neck presented grossly as a fatty, lobulated, brown, well demarcated, and encapsulated mass. X160.

LIPOSARCOMA

Liposarcomas are among the least encountered tumors afflicting the head and neck (fig. 133). Table 10 presents the anatomic sites of origin of 50 documented liposarcomas of the head and neck presented in the medical literature (sites in the skull, scalp, and meninges [9 patients] have been excluded). (Batsakis et al.).

The rarity of liposarcoma within the sinus and larynx precludes any generalization about their biologic behavior. The majority of head and neck liposarcomas have been myxoid liposarcomas. Including the cases arising in the skull, scalp, and meninges, 19 of 61 patients have died of their neoplasm — a mortality of 31 percent (Batsakis et al.).

An unusual case of intraosseous liposarcoma of the maxilla has been reported by Amarjit and associates.

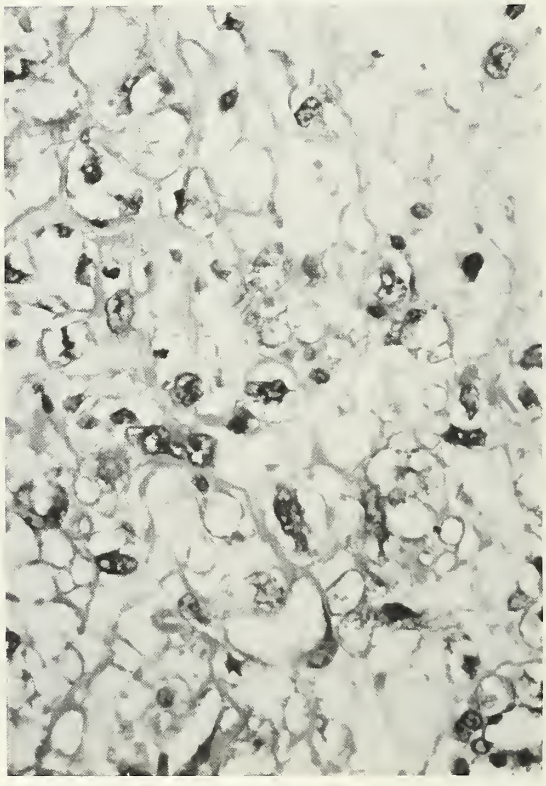

Figure 133
LIPOSARCOMA
This tonsillar, poorly differentiated liposarcoma shows anaplastic pleomorphic nuclei admixed with cells histologically supportive of fat type tissue. X400.

Table 10

ANATOMIC SITES OF ORIGIN OF LIPOSARCOMAS OF THE HEAD AND NECK

Site	No. Cases
Neck, pharynx, and parapharyngeal region	23
Cheek	8
Orbit	7
Soft Palate	4
Floor of mouth	3
Larynx	3
Lip	1
Mastoid	1

MYXOMA

SYNONYMS AND RELATED TERMS: Fibromyxoma.

Definition. A myxoma is a benign but often infiltrating neoplasm of uncertain cell origin, characterized by irregular, inconspicuous, round, spindle, or stellate cells within a matrix of abundant mucoid material, chiefly hyaluronic acid. There is scant vascularity and a variable meshwork of reticulum and collagen. Myxoma of the facial bone may have an abundance of collagen.

In the head and neck, two forms of myxoma occur: those arising in soft tissues and in skeletal muscle, and those arising in the facial bones (Canalis et al.; Kangur and Dahlin).

The myxoma of bone is a tumor of the facial skeleton. In extragnathic bones, the tumor is exceedingly rare, except as a component of chondromyxoid fibromas. The almost peculiar localization of intraosseous myxoma to the jaw bones has provided rationale for their origin from primordial odontogenic mesenchyme. Some believe they arise from an osteogenic embryonic connective tissue, while others regard both tissues as progenitors (Fu and Perzin, 1977).

The mandible is affected more than the maxilla and the sites of predilection are the posterior and condylar regions and the zygomatic process or alveolar bone of the maxilla (Farman et al.).

Incidence. Myxoma of the maxilla can present over a wide age period, with average age at discovery 33 years. There is no sex predilection. There were 26 patients with fibromyxoma (myxoma) diagnosed in the AFIP-OTR. They ranged in age from the first to eighth decades, with 7 patients in the pediatric age. They all involved a sinus (usually the maxillary antrum), with half also extending into the nasal cavity. There are also several cases arising in the middle ear area.

Clinical. The majority of the lesions are first noticed as a result of a slowly increasing swelling of the affected part. The lesions are generally painless and the mucosa is rarely ulcerated unless there has been trauma. When the antrum is not involved, there is usually considerable expansion of the maxilla. With extension, the antrum may become totally filled by the tumor. The majority of the lesions are multilocular radiolucencies with a "soapbubble" or "honeycomb" appearance. The majority of the tumors show no special association with teeth.

Gross. Myxomas are composed of gray to white multinodular tissue with a firm to gelatinous consistency. The lesions often have well defined borders, but no capsule.

Microscopic. Histologically, the typical lesion is characterized by scant, scattered, and often inconspicuous stellate or spindle cells in an abundant mucoid material which stains positive for mucopolysaccharides and has a rich network of delicate reticulin fibers (fig. 134). Odontogenic epithelium may or may not be found. The tumors infiltrate

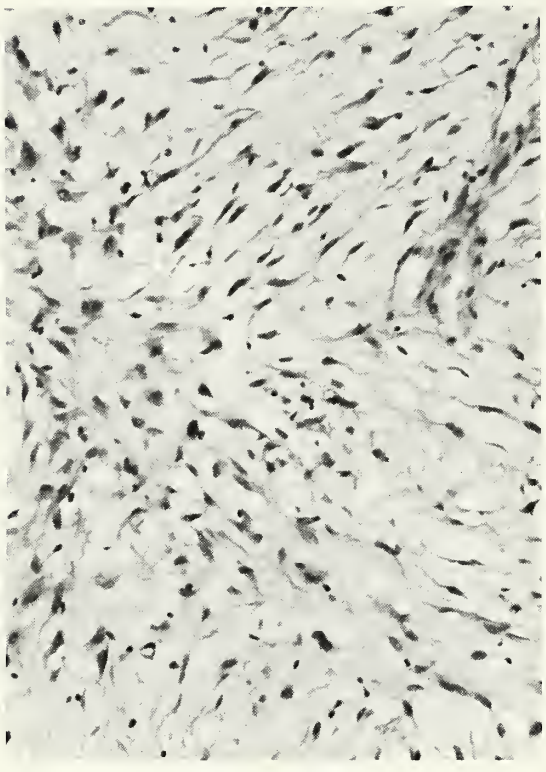

Figure 134
FIBROMYXOMA
Note the myxomatous micromorphology of this fibromyxoma of the maxillary sinus in a two year old boy. This is identical to the soft tissue myxoma. X400.

locally and bone can be replaced by the advancing tumor. Little or no new bone formation is seen at the infiltrating edge of the lesion.

Ultrastructural study reveals two basic cell types: secretory and nonsecretory. The secretory cell is the principal tumor cell and, in many respects, resembles the fibroblast.

Natural Histology. Myxomas of the jaw bones, while capable of considerable destruction, are only of local significance. Conservative excision with tumor free margins is the treatment of choice. Extensive surgical resection should be reserved for large or recurrent lesions.

Differential Diagnosis. Soft tissue inflammatory reactions, rhabdomyosarcoma, liposarcoma, and Schwann cell tumor constitute the most likely differential diagnostic alternatives. The immunoperoxidase antibody-antigen determinations should help with the problem of differential diagnosis.

Myxoma of the Soft Tissue

The myxoma of the soft tissue is a benign connective tissue tumor that is predominantly a lesion of the extremities. It has occurred in the paraoral soft tissues, pharynx, and larynx. An association of multiple myxomas and fibrous dysplasia has been noted (Wirth et al.).

Incidence. The tumors have been reported in newborns and patients in the eighth decade of life. There is no sex predominance.

Microscopic. The cell of origin is believed to be a fibroblast that has not differentiated sufficiently to lay down collagen, but is capable of producing acid mucopolysaccharides. The histologic and biochemical features closely resemble those of Wharton's jelly found in the umbilical cord. The tumor is sparsely cellular and vascular and contains an abundant mucinous substance. The ground substance stains faintly with mucicarmine and alcian blue stains and most of the mucinous material can be removed by prior treatment with hyaluronidase. The tumors are not well demarcated, but some may have a pseudocapsule.

Natural History. The tumors are slow-growing and may remain quiescent for long periods of time. Adequate local excision is not followed by recurrence or metastases. In short, the soft tissue myxoma, despite its local infiltration, pursues an essentially benign course (Elzay and Dutz).

Differential Diagnosis. It should be noted that many of the reported myxomas of soft

tissues, in reality, have been myxoid lipomas, Schwann cell tumors, and other soft tissue lesions manifesting myxoid changes (Elzay and Dutz). The immunoperoxidase determinations may be of differential help. There are several localized tumors of the glottic area of the larynx listed in the AFIP-OTR which conform to the histology and the localized benign behavior of the soft tissue myxoma. These vocal cord area tumors resemble the common polyp of the glottis, but they are usually larger and, when removed, may recur locally.

FIBROUS HISTIOCYTOMA

SYNONYMS AND RELATED TERMS: Histiocytoma; xanthoma; fibroxanthoma.

Definition and Pathogenesis. Fibrous histiocytoma is a generic term coined by Stout and Lattes. It applies to tumors composed of cells differentiating into fibroblastic and histiocytes and occurring in various tissues and organs. The diagnostic term is being widely applied to a number of benign and malignant lesions.

Tissue culture studies, as well as electron microscopic examination, have pointed to the tissue histiocyte as the most logical source of the so-called facultative fibroblast tumor cells. These cells have the light microscopic appearance and apparent collagen synthesizing ability of fibroblasts, thereby giving the impression of coexistence of histiocytic and fibroblastic elements in the same tumor (Ozzello and Hamels). Studies further suggest that both principal cell types (histiocyte-like and fibroblast-like cells) may derive from a single mesenchymal cell line.

The histologic interplay of the histiocyte and fibroblast yields a heterogenous and often bewildering spectrum of lesions, some neoplastic and others apparently of a reactive nature. In both categories, the lesion may be predominantly fibrogenic or manifest a pronounced epithelioid or histiocytic appearance.

Varieties. Morphologic variants of the basic fibroblast-histiocytic lesion, using the classifications of Kempson and Kyriakos and Soule and Enriques, may show benign behavior. These are listed as: nodular tenosynovitis (giant cell tumors of tendon sheath); dermatofibroma (sclerosing hemangioma, subepidermal nodular fibrosis); pigmented villonodular synovitis; atypical fibroxanthoma of skin; juvenile xanthogranuloma; xanthoma; and xanthofibroma. Variants listed as showing malignant or indeterminate behavior are: storiform fibrous xanthoma (dermatofibrosarcoma protuberans); retroperitoneal xanthogranuloma; fibroxanthosarcoma (malignant fibrous xanthoma-malignant fibrous histiocytoma); histiocytoma; and fibrous histiocytoma (unclassified). Other variants of the malignant fibrous histiocytoma include the pleomorphic sarcoma having numerous osteoclastic type giant cells (malignant giant cell tumor of soft parts) or abundant benign and malignant xanthoma cells (xanthomatous giant cell tumors, malignant xanthogranuloma).

Sites of Tumor. The head and neck region varies in its disposition for this group of lesions, ranging from the relatively common atypical fibroxanthoma of skin to the rarely occurring fibrous histiocytomas of the upper respiratory tract. Dahlin and associates have also described malignant fibrous histiocytomas of the facial bones and skull in six patients.

Incidence of Age. Blitzer and associates have reviewed the reported patients with fibrous histiocytoma of the deep structures of the head and neck. There was a mean age of 43 years, with a 3 to 1 male predominance.

Three of the tumors occurred in the ethmoid and maxillary sinuses, and one presented in the nasopharynx. The larynx and trachea accounted for three additional cases. The AFIP-OTR material reveals 65 patients with both benign and malignant fibrohistiocytomas involving the sinonasal tract, nasal vestibule, and adjacent skin area. There were 10 patients each with larynx and external auditory canal fibrohistiocytomas. The ages ranged from the first to the ninth decades, but the overwhelming majority occurred from the third to sixth decades.

Clinical Data. Fibrous histiocytoma involving the upper respiratory passages caused clinical problems similar to those produced by other soft tissue neoplasms affecting this area (nasal obstruction, a mass or swelling, epistaxis, loosening of teeth, or pain). Physical examination may show a mass projecting into the nasal sinus or oral cavity, facial asymmetry, proptosis, or a periorbital mass (Perzin and Fu).

Radiographic studies may demonstrate sinus opacification or cloudiness, a mass, or bone destruction.

Gross. The gross appearance may vary from a polypoid mass to large tumors filling the sinuses and eroding bone. Those involving the larynx are usually polypoid and ill-defined nodular masses. Most often, the tumors are yellow or partly so (Ogura et al.).

Microscopic. The histologic diagnosis of fibrous histiocytoma is based on the presence of certain distinctive findings (Perzin and Fu). There are areas in which the tumor cells have elongated, spindle-shaped nuclei with the appearance of fibrocytes or fibroblasts. These cells often produce a pattern which has been described as cartwheel, storiform, or spiral nebular. Elsewhere, the cells are found in a more fascicular pattern. Myxoid areas may also be identified. In addition, more rounded cells, often containing fine vacuoles in their cytoplasms and having the features of histiocytes, may be seen. Multinucleated giant cells (Touton giant cells) often with a foamy cytoplasm, may be found (fig. 135).

The proportion of fibroblast-like and histiocyte-like components varies greatly and some tumors may be composed predominantly of one or the other (fig. 136).

The cell population may also vary as far as their differentiation and anaplasia is con-

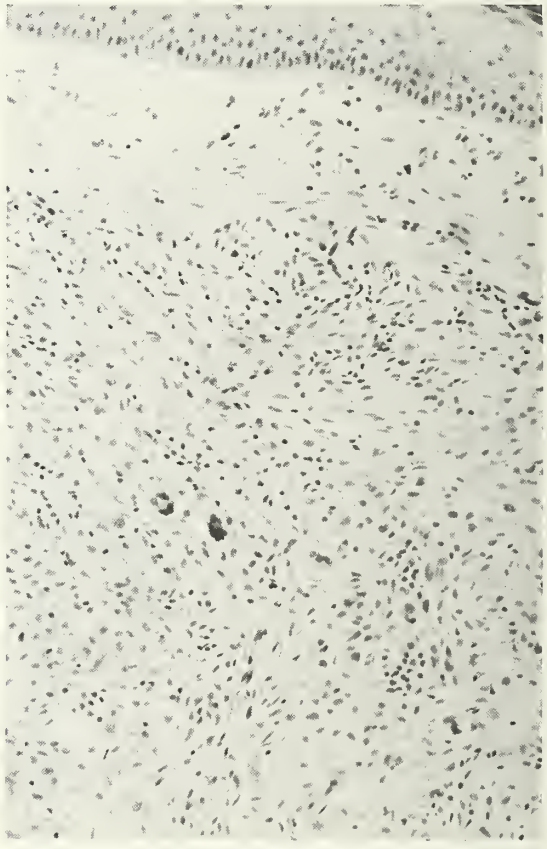

Figure 135
(Figures 135 and 136 are from the same patient)
HISTIOCYTOMA
This histiocytoma of the nasal vestibule presented as a skin-covered, orange macule. The histology reveals histiocytes with an occasional Touton (multiple nucleated) giant cell, with no limiting capsule to the lesion. X 63.

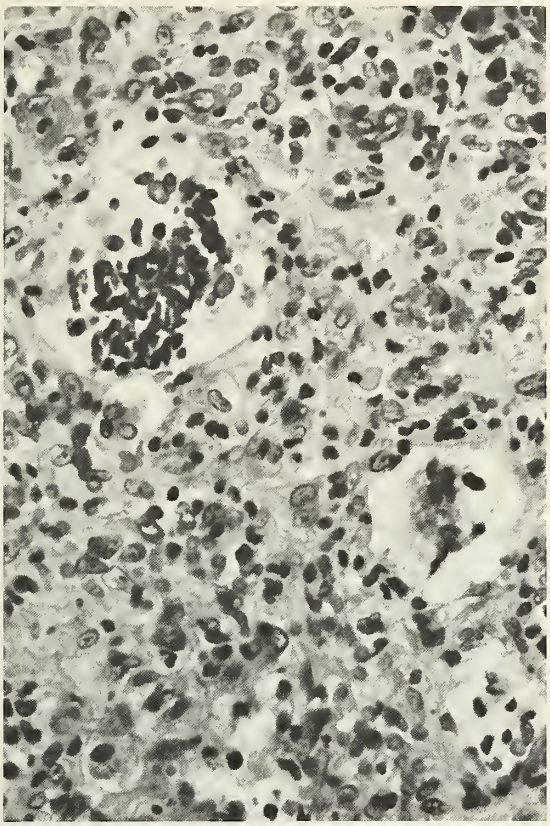

Figure 136
HISTIOCYTOMA
In this higher magnification of figure 135, note a spiral arrangement of the elongated nuclei with the appearance of fibroblasts. X160.

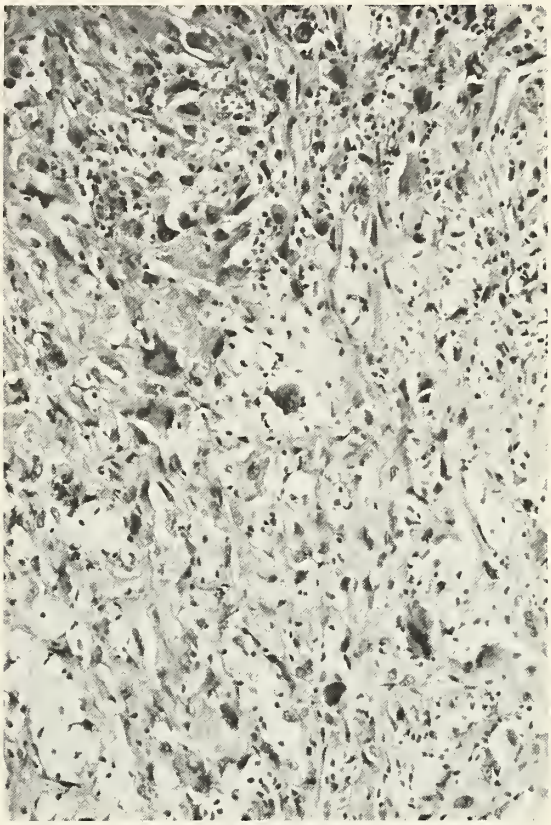

Figure 137
FIBROHISTIOCYTOMA
In this malignant fibrohistiocytoma of the maxillary antrum in a 60 year old man, there is extensive cellular pleomorphism, atypical mitosis, and malignant multinucleated cells. X160.

cerned. They may appear cytologically benign, with mature cells, no atypia, and no mitoses, or exhibit overtly malignant micromorphologic features.

Histologic criteria for malignancy have been proposed, but they lack a strict correlation with biologic behavior (Kempson and Kyriakos; Soule and Enriquez). These consist of anaplasia of stromal cells, extensive cellular pleomorphism, atypical mitoses, and diffuse and often intense neutrophilic infiltrate unassociated with necrosis (fig. 137). Occasionally, huge anaplastic giant tumor cells may lead to the strong consideration of rhabdomyosarcoma. Again, the immunoperoxidase examinations may help on this particular differential. The majority of metastasizing fibrous histiocytomas described in the literature have been large neoplasms growing in the deep soft tissues and showing anaplasia and mitotic activity on histologic examination. O'Brien and Stout found that the two features most associated with an aggressive nature are infiltrative margins and tumor size over 6 cm.

Natural History. Fibrous histiocytomas growing in the upper respiratory passages exhibit a spectrum of biologic behavior which

parallels that of other fibroblastic tumors, since most appear to represent local problems, but some do metastasize (Perzin and Fu). Blitzer and colleagues record a metastatic rate of 22 percent of histiocytomas of the head and neck and a recurrence rate lower than that expressed by other authors. It should be noted, however, that their follow-up periods were usually short.

SYNOVIAL SARCOMA

Frequency. Primary synovial sarcomas of an area other than the extremities are rare, but are being reported in the head and neck area with greater frequency. This is no doubt due to increased awareness of the neoplasms on the part of both clinicians and pathologists. Since 1954, when the first primary synovial sarcoma of the head and neck was reported, at least 60 additional patients with primary head and neck synovial sarcomas have been reported in the world's literature (Lockey; Roth et al.).

Sites of Tumor. Synovioblastic tissue is not plentiful in the head and neck and is not normally present in the retropharyngeal region, where many of the head and neck synovial sarcomas appear to take their origin. The neck does contain synovial tissue, not only in the tendinous portions of certain muscles, but also in the anterior portions of the larynx and pharynx (bursa subhyoidea, bursa laryngea subcutanea). These sources cannot be implicated in all cases and it is very likely that most of the sarcomas arise from synovioblastic differentiation of connective tissue.

The exact anatomic site of origin has been difficult to define from review of reported cases (Jacobs and Weaver; Krugman et al.; Lockey; Roth et al.). The parapharyngeal region (retropharynx and hypopharynx) is the most often cited location (Gatti et al.). This site is followed by "neck," particularly the anterior neck, larynx, pharynx, around the sternoclavicular and temporomandibular joints, cheeks, tonsils, and tongue (Shmookler et al.). In the latter area, the bursa of Boyer and the thyrohyoid ligament have been implicated.

Incidence. Synovial sarcoma is a neoplasm of young adults. Most of the cases have occurred in patients between the ages of 20 and 40 years. There is a suggestion that head and neck synovial sarcomas occur at a slightly younger age. Women appear to be affected more than men.

Clinical. Presentation is usually in the form of an ill-defined, deep-seated, and usually painless mass in the anterior neck. Associated pain or tenderness, said to be present in 40 percent of patients with synovial sarcoma elsewhere in the body, does not appear to be as prominent in the head and neck area. Other clinical signs and symptoms related to location may include hoarseness, dyspnea, and dysphagia.

Gross. The appearance of the neoplasm varies according to the location of the tumor and its relationship to adjacent structures. As a rule, the tumors are well circumscribed and often pseudoencapsulated. They may be spherical, multinodular, or lobulated, and in the head and neck all have been solitary, painless masses (Krugman et al.). Some have a long pedicle attaching the neoplasm to the mucosa.

At the time of discovery, the size of the neoplasms has varied from 1 to 10 cm, with a median of 5 cm. They are usually soft to rubbery and, on section, are yellow to yellow gray. Hemorrhage and focal necrosis are not unusual. Some may have a mucoid or gelatinous consistency in areas. Microcystic areas may be in evidence. A slightly fibrous,

finely whorled pattern, accentuated after formalin fixation, may predominate. Gritty flecks of calcification are also encountered in many of the tumors when cut. These foci may be discernible in radiographs of the gross specimens.

Microscopic. The histopathologic appearance of a synovial sarcoma is the same whether in the head and neck or extremities or in children or adults. It may be a biphasic lesion or one that is uniphasic (figs. 138, 139). In the former, epithelioid cells are arranged in nests or pseudoacini and surrounded by fibrosarcoma-like cells. The synovial-like cells are often pleomorphic and line spaces, clefts, or cysts. The biphasic pattern is accentuated by reticulum stains. The pseudoglandular spaces contain granular or acidophilic material. This material is positive with the periodic acid-Schiff (PAS) stain, magenta with acid mucopolysaccharide (AMP) and alcian blue staining, and pink with the mucicarmine stain. None of these reactions are abolished with pretreatment with testicular hyaluronidase. Hyaluronidase sensitive mucoid material is present in the stroma surrounding the pseudoglandular spaces.

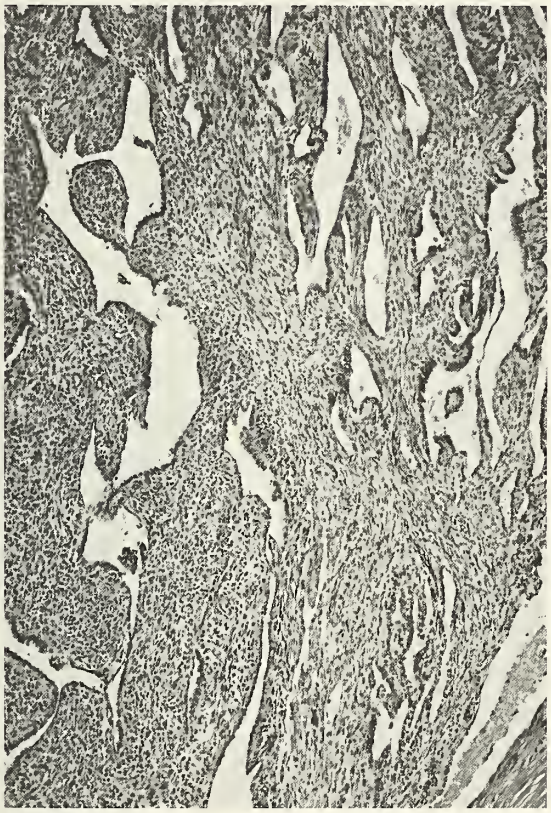

Figure 138
(Figures 138 and 139 are from the same patient)
SYNOVIAL SARCOMA
This pharyngeal area synovial sarcoma emphasizes the biphasic histology of epithelioid cells arranged in nests or pseudoacini and surrounded by fibrosarcoma-like cells. X63.

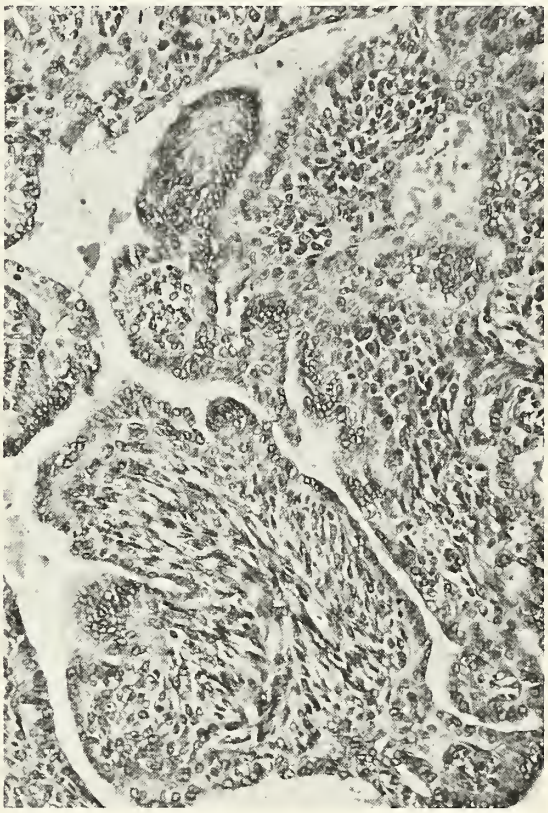

Figure 139
SYNOVIAL SARCOMA
Higher magnification of figure 138 shows slit-like and pseudoglandular spaces lined by epithelioid-appearing cells. X160.

Contrasting with the biphasic pseudoglandular, fibrosarcomatous pattern, a synovial sarcoma may present with a picture approximating a fibrosarcoma or leiomyosarcoma, leaving only a few areas of epithelioid cells as evidence of synovioblastic origin (fig. 140). Discovery of these foci may require diligent examination of multiple sections. A recent innovation that has proved quite helpful in arriving at the diagnosis of synovial sarcoma in AFIP-OTR material is the keratin positivity of the neoplasms when utilizing the immunoperoxidase studies. Some of the poorly differentiated synovial sarcomas may be richly vascular and closely resemble malignant hemangiopericytoma. Vascular invasion may be manifest.

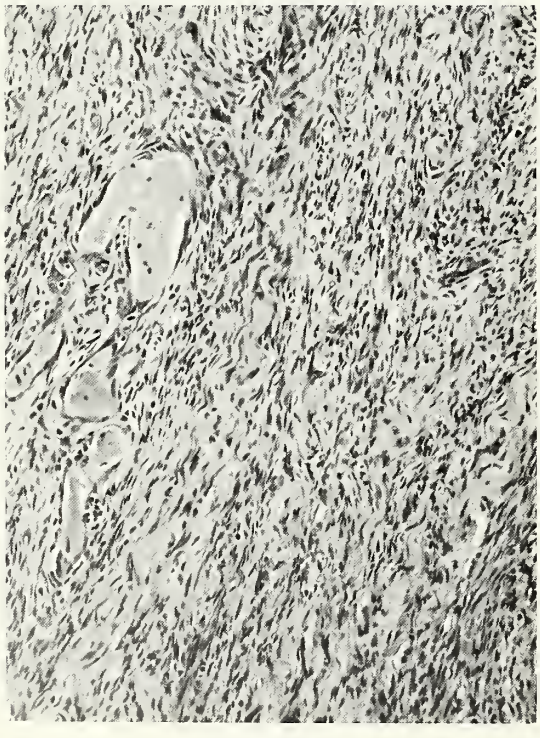

Figure 140
SYNOVIAL SARCOMA
This synovial sarcoma of the larynx essentially consists of a uniphasic, spindle cell, sarcomatous histology with several glandlike structures on the left considered to be the epithelioid element. X160.

Dystrophic calcification and calcospherites, a characteristic finding in synovial sarcoma regardless of location, is seen in slightly more than one-half of all synovial sarcomas of the head and neck.

Another important ancillary histopathologic finding is the abundance of mast cells. These are particularly found in well differentiated biphasic tumors and in fibrosarcomatous areas undergoing fibrosis.

Electron Microscopy. Electron microscopy supports the synovioblastic origin of these sarcomas (Roth et al.). The typical case at the ultrastructural level is biphasic. All studies identify distinct basal lamina between the "epithelial" and stromal components of the tumor. The epithelioid type cells reveal multiple cell attachments (maculae adherens), microvilli intercellular spaces, free ribosomes, arrays of endoplasmic reticulum, a prominent Golgi apparatus, and small vesicles. The fibroblast-like cells are associated with variable amounts of extracellular material and mature collagen.

Treatment and Prognosis. A firm conclusion regarding optimal treatment is not possible from the studies of various series dealing with head and neck synovial sarcomas, but, overall, an adequate surgical approach would seem to afford the greatest likelihood of long-term survival (Shmookler et al.). Irradiation and chemotherapy have been utilized with questionable results. From reports of cases with adequate followup, there is evidence that synovial sarcoma of the head and neck is less aggressive than one arising in the extremities. Roth and associates, however, report a 47 percent five-year postsurgical survival for head and neck synovial sarcomas, which is very little different from the survival given by others for peripheral synovial sarcomas. In Roth and associates' series, 12 of 22 followed patients died

from their disease, 11 within a period of one to eight years after therapy. Ten of these patients had pulmonary metastases at the time of death. Cadman and colleagues, studying peripheral synovial sarcomas, record that metastases occurred to the lungs in 81 percent of patients, regional lymph nodes in 23 percent, and bones in 20 percent. Head and neck synovial sarcomas do not appear to share this predilection for regional lymph node and osseous metastases.

It has been suggested that a biphasic pattern imports a better prognosis than a predominating monophasic or epithelial pattern. We are not of that conviction and consider size and location of the tumor to be more pertinent.

EWING'S SARCOMA

Sites of Tumor. This uncommon, highly aggressive neoplasm presents in skeletal and extraskeletal forms. In the jaws, the neoplasm involves mainly the mandible, in particular, the horizontal ramus. It is less often found in the maxilla, and is even more rare in other facial or skull bones (Ferlito). Extraskeletal forms in the head and neck are even less common, occurring primarily in the soft tissues of the face and neck and the sinonasal tract. Pontius and Sebek have reported a single case arising in the nasal fossa.

Incidence. The tumor presents predominantly in males and during the first decades of life. Those of the maxilla tend to occur in slightly older people (Ferlito).

Clinical. Nasal obstruction, pain, swelling, and displacement of regional structures are the prevalent signs and symptoms. Because of the mistaken diagnosis of sinusitis, diagnosis is often delayed.

Ewing's sarcoma of the jaws presents radiographic features similar to those seen in involvement of the peripheral skeleton. These include permeative destructive pattern, periosteal reaction which may be a lamellated type, and adjacent soft tissue involvement (deSantos and Jing).

Microscopic. Ewing's sarcoma is a highly cellular neoplasm with little supporting stroma except for widely separated strands of fibrous tissue. The cells may be arranged in nestlike groups or be diffuse in architecture. The cells are generally of a uniform size, with scanty, poorly delineated cytoplasm. Nuclei are round to oval with a somewhat ground-glass appearance of their finely dispersed chromatin (figs. 141, 142). There may

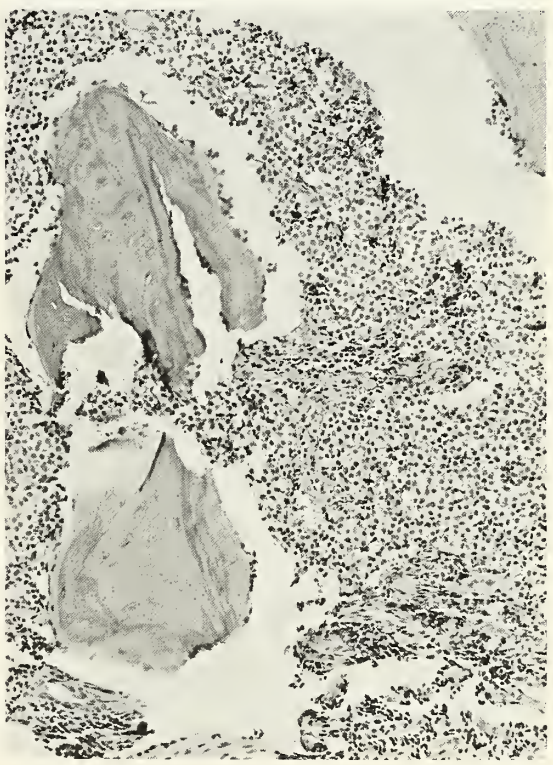

Figure 141
(Figures 141 and 142 are from the same patient)
EWING'S SARCOMA
In a biopsy of a destructive mass in the right maxillary sinus felt histologically most consistent with Ewing's sarcoma, the cells are uniform with a round to oval nucleus and scant, poorly delineated cytoplasm. X63.

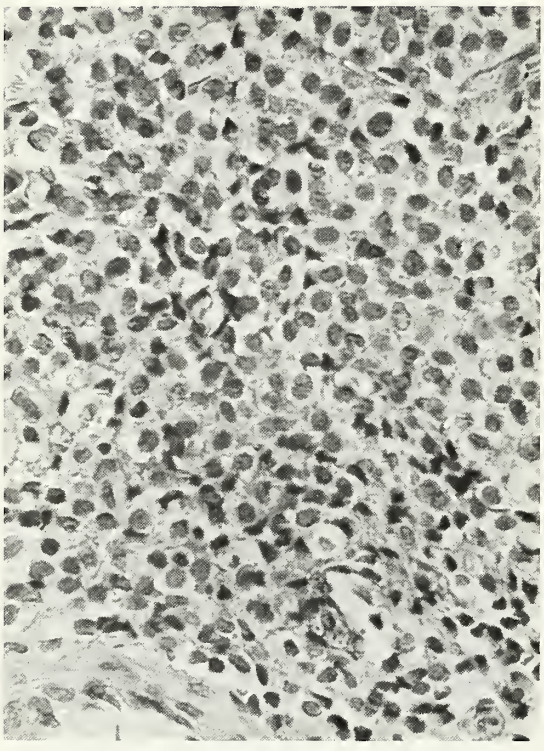

Figure 142
EWING'S SARCOMA
In this higher magnification of the previous figure, the nuclei are oval to round, with a somewhat ground-glass appearance of their finely dispersed chromatin. X250.

be abundant intracytoplasmic glycogen and its presence will serve to exclude lymphoma, but glycogen can also be found in neuroectodermal tumors and rhabdomyosarcoma. Electron microscopy may provide the most reliable diagnostic tool with the Ewing's tumor cell by revealing few organelles with only occasional mitochondria and sparse endoplasmic reticulum, whereas the ultrastructural study of the neuroectodermal tumors and rhabdomyosarcomas will certainly reveal a much more specific diagnostic cytologic pattern. Also, a most characteristic feature of the Ewing's tumor is abundant glycogen rosettes (Friedman and Gold).

Differential Diagnosis. Differential diagnosis includes nearly all small cell malignant neoplasms presenting in the facial bones, such as lymphoma, neuroblastoma, olfactory neuroblastoma, retinoblastoma, rhabdomyosarcoma, and undifferentiated carcinoma.

Treatment and Prognosis. Combined therapy with radiation followed by cyclic chemotherapy is now the recommended treatment of Ewing's sarcoma. With this form of management, the dismal prognosis of the tumor may be changed (Chan et al.). Five-year survival is low and most patients die of hematogenous dissemination (lungs, liver, and bones).

ALVEOLAR SOFT PART SARCOMA

The alveolar soft part sarcoma, an infrequently encountered neoplasm, is rare in the head and neck, where the base of the tongue has been the site of predilection (Spector et al.). Primary involvement of the airway has not been reported.

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VASCULAR TUMORS

There is only one distinctive vascular lesion in the head and neck: the angiofibroma. The remainder, be they vascular malformations, aftermath of trauma, or neoplasms, are more plentiful in the external soft tissues and skin than in the airway.

Angiomatous (blood vascular and lymphatic) malformations, epitomized by the cystic hygroma, may have ramifications into the nasal, paranasal, and laryngeal structures. Arteriovenous communications, either post-traumatic or congenital, may behave in a similar fashion. In these instances, airway involvement is usually fortuitous. The following discussion relates to those vascular lesions that manifest an intrinsic involvement of the airway.

ANGIOFIBROMA

SYNONYMS AND RELATED TERMS: Juvenile nasopharyngeal angiofibroma.

Definition. An angiofibroma is a locally destructive tumor composed of fibrovascular tissue of varying maturity, arising in or adjacent to the wall of the nasopharynx.

Despite the long history of this lesion, very likely back to Hippocrates, and despite the great number of investigations and publications related to pathogenesis and treatment, considerable differences of opinion still exist about facets of this tumor.

Incidence and Frequency. As Harrison points out, one of the few grounds of common agreement is that the average age of diagnosis is around 14 years, with a range between 7 and 21 years. He also cites an occurrence in a baby of 5 weeks, and there have been reports of presentation in older men. It is very rare for the tumor to arise over the age of 25 years.

Although there are claims of completely authenticated cases in female patients, the overwhelming majority certainly occur in males. One angiofibroma in a female has been studied with the electron microscope and found to be similar ultrastructurally to those in males (Svoboda and Kirchner). Fitzpatrick has studied the genetic pattern of two female suspects without finding any defect. There is no case of diagnosed nasopharyngeal juvenile angiofibroma in a female in the AFIP-OTR material.

The discovery of an angiofibroma after the age of 25 years usually indicates the presence of a subclinical tumor over the preceding decade. There are, however, examples where the preceding history is short-lived. A particularly interesting case has been presented by Kwik and associates. Their 49 year old patient had been receiving testosterone therapy.

Angiofibromas occur in any country, with a rather wide range of incidence. At the Royal National Throat, Nose and Ear Hospital in London, the incidence rate was 1 patient per 150,000 ENT admissions (Harrison). Patterson gives a reported incidence in the United States of 1 in 6000 to 1 in 16,000 ENT patients.

Pathogenesis and Sites of Origin. The tissue of origin remains controversial and many theories are now only historical (Girgis and Fahmy). Most likely, the tumor arises from the distinctive fibrovascular stroma normally present in the nasal cavity and nasopharynx. Frequently, the angiofibroma duplicates this tissue (Fu and Perzin).

The site of origin is usually broadly based and situated on the posterolateral wall of the nasal cavity where the sphenoidal process of the palatine bone meets the horizontal ala of the vomer and the pterygoid process. This forms the superior margin of the sphenopalatine foramen and the posterior end of the middle turbinate, thus explaining the ease with which the spread occurs to sphenoid, nasopharynx, and pterygomaxillary tissue and fossa (vide infra). Because of the tumor's secondary attachments with additional blood supply and spreading capabilities, it is erroneous to restrict the site to the nasopharynx. Bona fide paranasal angiofibromas have been reported by Hora and Brown and by Krutchkoff and associates.

Clinical History. A description of the natural course of an angiofibroma has been provided by Neel and colleagues. The tumor first grows beneath the mucosa just inside the posterior choanal margins on the roof laterally. With increasing size, there is submucosal extension along the roof to the posterior border of the septum and, thence downward, thus forming a mass in the roof of the posterior nasal cavity. The nasal cavity is then filled, crowding the septum into the opposite nasal cavity and compressing the turbinates. Neel and associates point out that the tumor does not enter the maxillary sinus through the lateral wall of the nose, but comes out of the posterior choana, where it may fill the nasopharynx, displace the soft palate, and be visible below its free edge. Destruction of the medial wall of the antrum also may occasionally occur. Lateral growth is through the sphenopalatine foramen with expansion of the posterior end of the middle turbinate.

Once into the pterygomaxillary fossa, the tumor presses on the surrounding bony walls and destroys the root of the pterygoid process of the sphenoid bone. The bulging of the cheek that is often an accompaniment of the angiofibroma is preceded by extension into the infratemporal fossa and expansion of the pterygomaxillary fissure.

If the tumor is sufficiently large, it may bulge into a lower part of the temporal fossa and produce a swelling above the zygoma. Following this, the tumor usually moves into the inferior orbital fissure, which opens into the upper anterior third of the pterygomaxillary fossa and enters the lower end of the superior orbital fissure, which meets the interior orbital fissure in the posterosuperior wall of the pterygomaxillary fossa. At this site, the angiofibroma destroys the great wing of the sphenoid bone. This produces characteristic widening along the lower lateral margin of the superior orbital fissure and proptosis. The lesion enlarges in the pterygomaxillary and temporal fossae, destroying the base of the pterygoid process. Destruction of this bone brings the angiofibroma against the dura of the middle cranial fossa, anterior to the foramen lacerum and lateral to the cavernous sinus.

The above extensions are possibly concomitant with growth of the tumor from its point of origin through the floor of the sphenoid sinus. Continued expansion from this point fills the sinus and, eventually, the sella turcica. Thus, the angiofibroma may enter the cranial cavity in the middle fossa either anterior to the foramen lacerum and lateral to the cavernous sinus and carotid artery, or through the sella medial to the carotid artery and lateral to the pituitary, or by both paths. For a lesion not yet definitely accepted by all as neoplastic, it clearly manifests histologic aggressiveness.

Clinical. The presenting signs and symptoms of the angiofibroma have been well characterized. They are those of an obstruc-

tive, well vascularized mass occupying the posterior nares, producing nasal obstruction together with intermittent epistaxis. Extension into the orbit results in proptosis and diplopia. If the tumor extends as far as the posterolateral margin of the maxilla, swelling of the face can occur. Despite the severity of these signs and symptoms, over one half of recently reported patients had significant signs and symptoms for over a year prior to diagnosis.

The age and sex incidence combined with historical evidence and radiographic findings should preclude hazardous biopsy of the tumor.

Radiographic. The plain film and angiographic appearance of these tumors is characteristic. On the plain films, "bowing" of the posterior wall of the maxillary sinus is the most consistent and reliable finding. The carotid arteriographic appearance is consistently typical and can be relied upon for diagnosis (Sessions et al.; Den Herder). The lesion may be seen most clearly on lateral and vertico-submental views. Angiographic studies not only yield a characteristic picture, but are invaluable for definition of the exact extent of the tumor and for delineation of the feeding vessels in order to determine if there is one-sided or bilateral vascularization. The pattern of vessels is rather characteristic in the arterial phase, where filling of an excessive number of dilated and tortuous vessels occurs. In the capillary phase, the configuration changes to a homogeneous vascular staining demonstrating the extent of the tumor. The angiographic pattern closely resembles that of a meningioma.

Studies with angiography and subtraction technic demonstrate that the main blood supply of most angiofibromas comes from an enlarged internal maxillary artery. Supply from both sides may be shown, particularly when the external carotid artery has been ligated. Arterial supply has been identified from dural, sphenoidal, and ophthalmic branches of the internal carotid, the vertebral artery, and thyrocervical trunk (Neel et al.).

Gross. Grossly, the tumor is located on one side or the other of the posterior nares and nasopharynx or it may completely fill the nasopharynx. A considerable number already have extensions into paranasal regions at the time of diagnosis. These include the sphenoid, ethmoid and maxillary sinuses, the retroantral space, orbit, and intracranial space. The tumor is usually described as pink-gray to purple-red, lobulated, and rubbery. Ulceration of the overlying mucosa is uncommon. More often sessile than polypoid, it is unencapsulated and infiltrates surrounding tissue. Because of their wide base of origin and secondary attachments, resection in continuity may be impossible. Occasionally there may be only a narrow attachment stalk.

Microscopic. The angiofibroma is composed basically of two components — a characteristic fibrous stroma and vascular channels of variable size, lined by flat endothelial cells (fig. 143). The blood vessels in these tumors do not have elastic fibers in their walls. The smooth muscle coats of the larger vessels are usually irregular or incomplete. The smaller vascular channels have no smooth muscle.

The stroma is made up of a fibrous matrix of fine and course collagenous fibers. Connective tissue cells interspersed in this matrix vary in size and shape. The stellate-shaped cell (fibroblast and myofibroblast) is quite characteristic (fig. 144). Mast cells are characteristically present. Mucoserous glands, unless invaded, are not found in the angiofibroma.

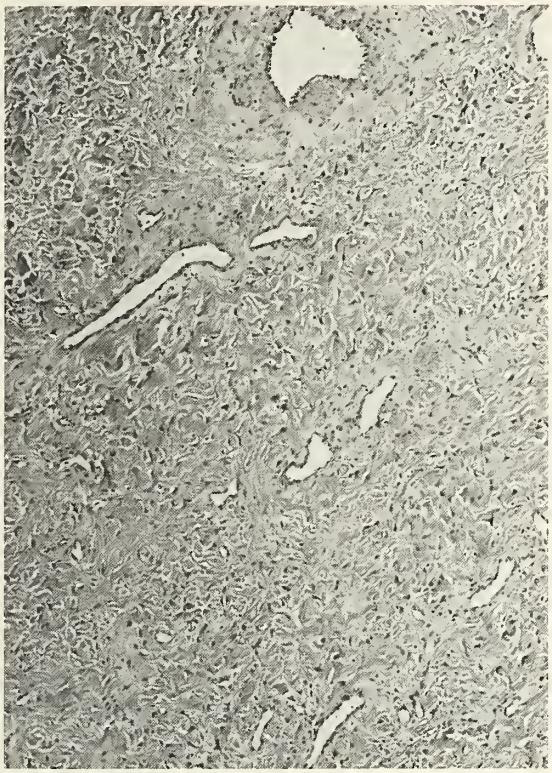


Figure 143
(Figures 143 and 144 are from the same patient)
ANGIOFIBROMA
This angiofibroma exhibits a bland stroma with scattered slit-like and oval vascular spaces. X63.

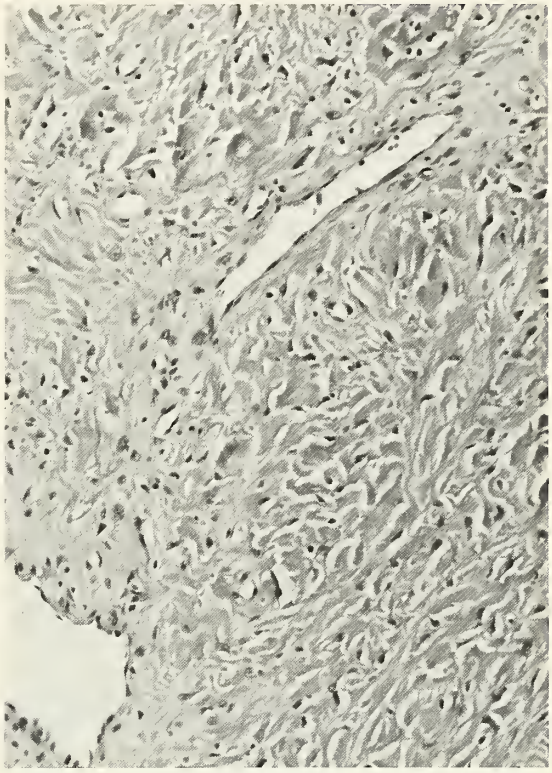


Figure 144
ANGIOFIBROMA
In this higher magnification of figure 143, the collagenous fibrous stroma reveals scattered stellate-like fibroblasts. X160.

In all tumors there is an admixture of stromal and vascular components. In younger, rapidly growing lesions, the vascular pattern is outstanding; in older lesions, the fibrous stroma dominates the picture (Hubbard). This histologic relationship has not been uniformly accepted. There is considerable variation in the vascular pattern in different tumors and even within the same tumor. Basically, however, large and small thin walled vessels are seen separated by a variable amount of stroma. The endothelial cells of the medium and large sized vessels are flattened and thin, while in the smaller, more actively growing vessels, the endothelium may be plump and hypertrophic. In some areas, usually near the mucosal surface, a diminution of the caliber of the vessels is seen until a pattern suggestive of sclerotic hemangioma is imparted.

A myxomatous type of change is not infrequent in the stroma, but this is usually focal and never as diffuse as seen in a nasal polyp. A capsule is not found, but partial enclosure or confinement of the tumor may occur by compression of connective tissue, thus separating the tumor from the overlying mucous membrane.

The stellate fibroblasts may have a tendency to radiate about vessels. Reticulum stains show a diffuse network, each cell being surrounded by bands of fibers. There

are no elastic fibers or smooth muscle fibers demonstrable by histochemical means. Vascular thromboses and perivascular fibrin deposition are frequent. The overlying mucosa may be denuded and is more often of a metaplastic squamous cell than respiratory type.

Electron microscopic evaluation has raised new possibilities concerning the stromal cells in the angiofibroma (Stiller et al.; Taxy; Battifora and Applebaum). Numerous round, electron dense inclusions of uncertain compositions have been demonstrated in the nuclei of stromal cells. The ultrastructural identity of the stromal cell as a fibroblast (on the basis of collagen production, a well developed rough endoplasmic reticulum [RER], and intracytoplasmic filaments) has been challenged by Taxy, who raises the possibility that the cells may be myofibroblasts. Support for this idea has been given by Stiller and associates. These workers subdivided the fibroblasts on the basis of their organelle content: (1) activated "classical" fibroblasts; (2) activated fibroblasts with resemblance to histiocytic-like cells due to subplasmalemmal vesicles and lysosomal bodies; and (3) fibroblasts with a myoid differentiation. The latter range in appearance from typical myofibroblasts to cells indistinguishable from smooth muscle cells. The same investigators consider that cells of the capillary vessel may change into stromal cells.

By light microscopy, the effects of exogenous estrogen administration on the tumor may be summarized as follows: (1) the increased collagenization of the stroma; (2) a decrease in blood vessels; and (3) an increase in the thickness of blood vessels with attenuation of the endothelia.

Natural History. The natural history of angiofibroma is one of progression with increase in both growth and symptoms. There is little reliable evidence of so-called spontaneous involution.

The existence of a sarcomatous form of angiofibroma is denied by most authors. The cases reported by Batsakis and associates and Hormia and Koskinen, however, appear to be substantiated. In the former, radiation was considered the provoking stimulus. In the latter patient, an 8 year old boy, metastases occurred to regional lymph nodes and bone. This complication of angiofibroma must be considered as nearly negligible.

The contemporary management and evolution of treatment has been considered by Harrison and by Boles and Dedo.

HEMANGIOMA

Of the vascular lesions of the nasal cavity, paranasal sinus, nasopharynx, and larynx, the benign hemangioma is the most frequently encountered. They may be subdivided into capillary, cavernous, and venous forms (Fu and Perzin).

Capillary Hemangioma of the Sinonasal Tract

SYNONYMS AND RELATED TERMS: Pyogenic granuloma; granulopyogenicum; angiogranuloma; hemangioma of granulation tissue type; lobular capillary hemangioma; benign hemangioendothelium.

The main problem with this essentially benign vascular tumor entity is whether it represents a true neoplasm (hemangioma) or a reactive tumefaction (pyogenic granuloma). The question is academic, as all will agree as to the benignity and local assured surgical removal for both entities. Fechner and associates feel the lobular pattern of the capillary nasal or oral area lesions supports the term of lobular hemangioma, while in the larynx, the nonlobular architecture and ad-

mixture of inflammatory cells and ulceration supports a diagnosis of granulation tissue. They consider the latter condition as strictly a post-traumatic lesion. The capillary type hemangiomatous tumor is the most common vascular pattern seen in the upper respiratory tract, particularly the nasal cavity. The lesion is rarely discovered as an incidental finding, since epistaxis and nasal obstruction will bring the patient to a physician within one year of the onset of symptoms. They are most often found in the anterior nasal septum (Little's area or Kiessalback's triangle), followed by the turbinates (most often at the tip of the turbinate).

Age and Sex. Fechner and associates pointed out that the so-called lobular hemangioma of the nasal and oral cavity had a predilection for males less than 18 years of age and women between the ages of 18 and 39 years. The experience of the AFIP-OTR suggests that this type of vascular tumor is rarely observed in patients who are less than 16 years of age. Most of the AFIP-OTR patients are in their fourth and fifth decades of life. There is apparently no significant sex preference.

Gross. Hemangiomas are usually polypoid, pedunculated nodular masses with a lobulated and smooth surface. They rarely exceed 2.0 cm and are usually less than 1.5 cm in major dimension.

The so-called hemangioma of pregnancy (granuloma gravidarum) may also present in the anterior nasal septum. This tumor is indistinguishable from the usual capillary hemangioma or granuloma pyogenicum.

Microscopic. Occasionally, a polypoid vascular lesion of the sinonasal cavity will reveal a nest of small, uniform, vascular channels with flattened endothelium and a pink homogenous stroma (fig. 145), but the majority will suggest a central larger vessel with small branchlike tributaries into the surrounding area, supporting the idea of a reactive origin (figs. 146, 147). Quite often the endothelium may be prominent, with rare mitotic figures and possible "tufting." This form may suggest the so-called benign hemangioendothelioma, which is difficult to

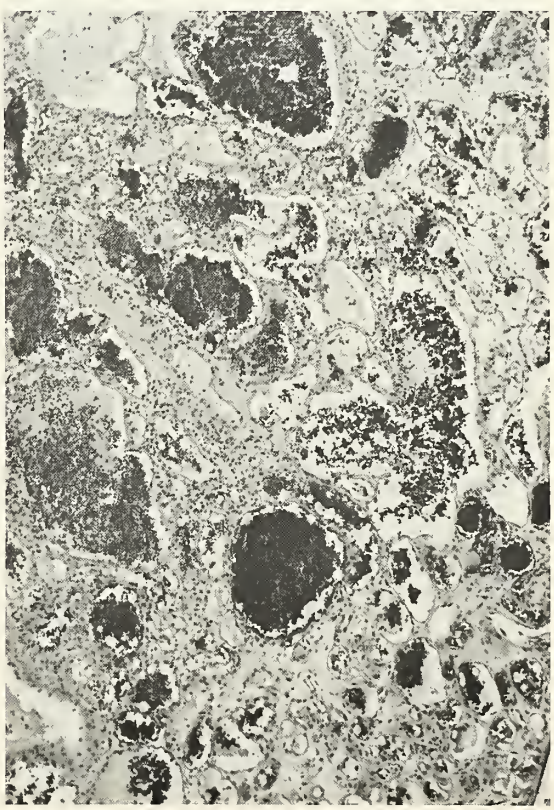


Figure 145
HEMANGIOMA
This exceptional hemangioma of the sinonasal tract area has more or less uniform vascular channels. X63.

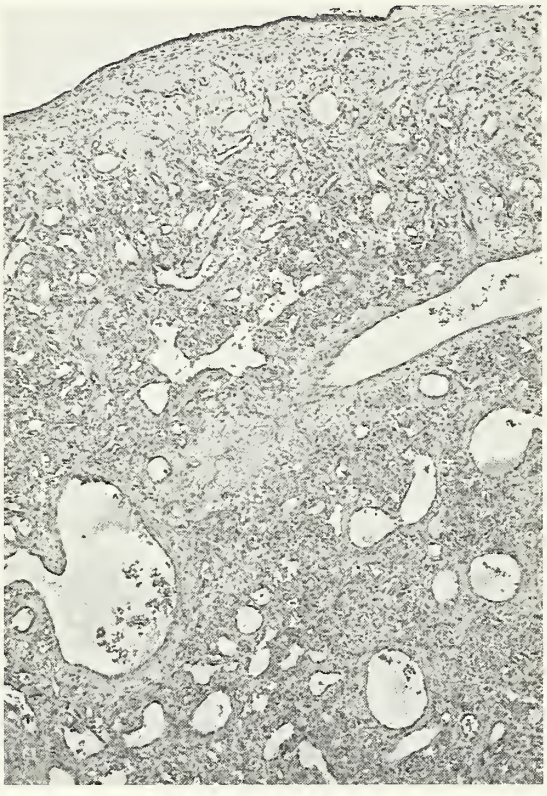


Figure 146
(Figures 146 and 147 are from the same patient)
HEMANGIOMA
The architecture of this hemangioma of the nasal septum supports a central large vessel with surrounding suggestive feeder vessels. This is the histology that some accept as that of a pyogenic granuloma. X63.

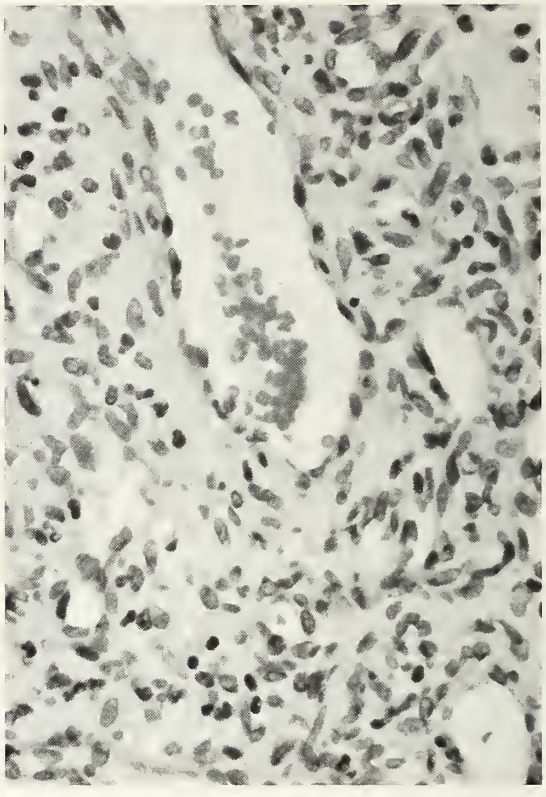


Figure 147
HEMANGIOMA
In this higher magnification of the previous illustration, the intervascular stroma shows plump spindle cells oriented around the vessel wall. X400.

separate clinically or histologically from the capillary hemangioma. The intervening stroma will usually contain spindle-like cells that are concentrated around the vessels. When there is necrosis, inflammatory infiltrate, and surface ulceration, the tendency to consider these as reactive pyogenic granuloma is greatest. The absence of inflammation and an overlying metaplastic squamous cell mucosa is certainly not unusual, however.

These vascular tumors of this anatomic region are cured usually by local excision, with a rare recurrence. There is a tendency for the hemangiomas of pregnancy (granuloma gravidarum) to regress after parturition.

Hemangioma of Facial Bones

There are several cases of histologically benign vascular tumors in the AFIP-OTR data that are completely confined to the facial bones, particularly to the maxillary sinus wall. These tumors can be quite disfiguring, as well as causing obstruction and local destruction. The histology is that of benign vascular tumor occupying the narrow spaces (fig. 148). The therapy recommended is surgical removal, which can be a difficult task.

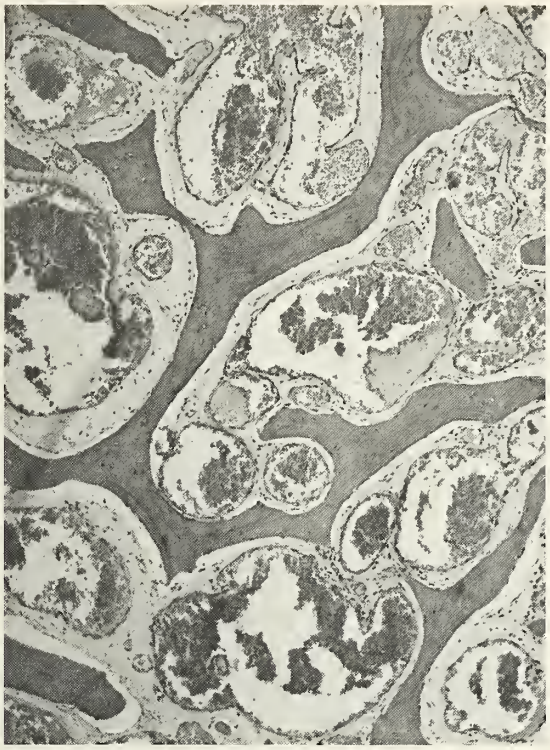


Figure 148
HEMANGIOMA
A portion of a hemangioma of the bone of the anterior maxillary sinus wall. X63.

INTRAVASCULAR PAPILLARY ENDOTHELIAL HYPERPLASIA

SYNONYMS AND RELATED TERMS: Intravascular vegetating hemangioendothelioma; intravenous pyogenic granuloma; Masson's pseudoangiosarcoma.

Definition. Intravascular papillary endothelial hyperplasia is a benign intravascular process that bears a striking histologic resemblance to angiosarcoma (Corio et al.). Histologically, a similar process is seen in organizing hematomas of the sinonasal tract. The lesions affect the subcutaneous tissue throughout the body as well as the oral-perioral area (Corio et al.) and the sinonasal tract area. The 14 patients reported by Corio and associates had an age range from 21 to 72 years (mean 44.6 years). Ten were males. The lesion presents as a blue to red mucosal skin-covered nodule with a prediagnosis history of two weeks to eight years (usually less than four months). The gross pathology is represented as a multicystic well circumscribed hemorrhagic soft tissue mass with the size varying from .3 to 8.5 cm (average 3.0 cm) (fig. 149). The microscopic picture is that of an invasion of a dilated endothelial lined, apparently venous structure, with thrombotic and endothelial proliferation (fig. 150). The papillary structures contained a central core of hyalinized thrombus covered by endothelial cells. Occasionally, these papillary structures fused to form an interlacing anastomosing vascular network that was separated in some areas by bands of fibrous tissue. Sometimes exuberant proliferations of apparent endothelial cells could be seen. Abnormal mitosis is usually not seen, but an increased mitotic index (2 to 3 mitotic figures per HPF) is present. Inflammatory cells are usually absent, but eosinophils may be abundant. The case report of Ulbright and Santa Cruz is described as a pyogenic granuloma in the vessel lumen with some involvement of the vessel wall, suggesting possible origin from the vasa vasorum.

Organizing hematomas and infarcted inflammatory polyps can cause some confusion in the differential diagnosis of vascular lesions of the sinonasal cavity. The risk is overdiagnosis as a neoplasm, particularly a malignant vascular proliferation. The tumors are seen by the clinician as a sessile mass, usually on the lateral wall of the nose. Histologically, the impression is one of a tumor formed of irregular blood vessels lined by bizarre endothelial cells. The true diagnosis is suggested by the presence of blood and blood products along with the revascularization process.

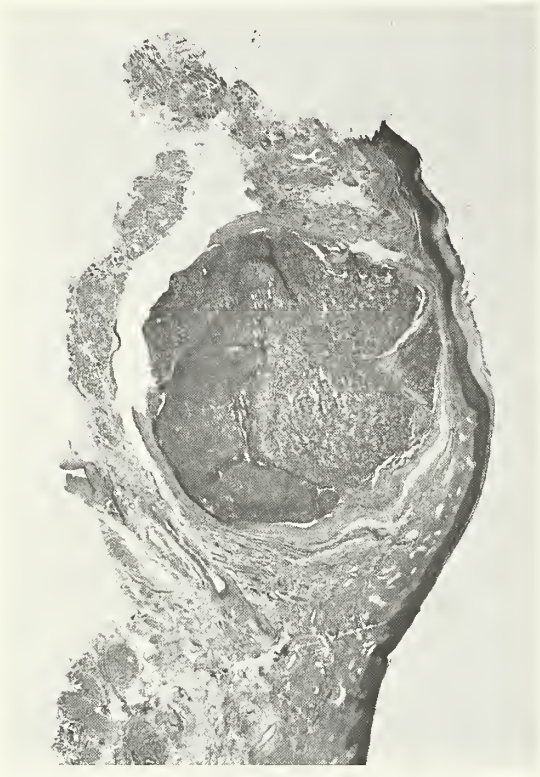


Figure 149
(Figures 149 and 150 are from the same patient)
INTRAVASCULAR PAPILLARY ENDOTHELIAL HYPERPLASIA
This subcutaneous skin lesion of an intravascular papillary endothelial hyperplasia was removed from the lip area. X6.

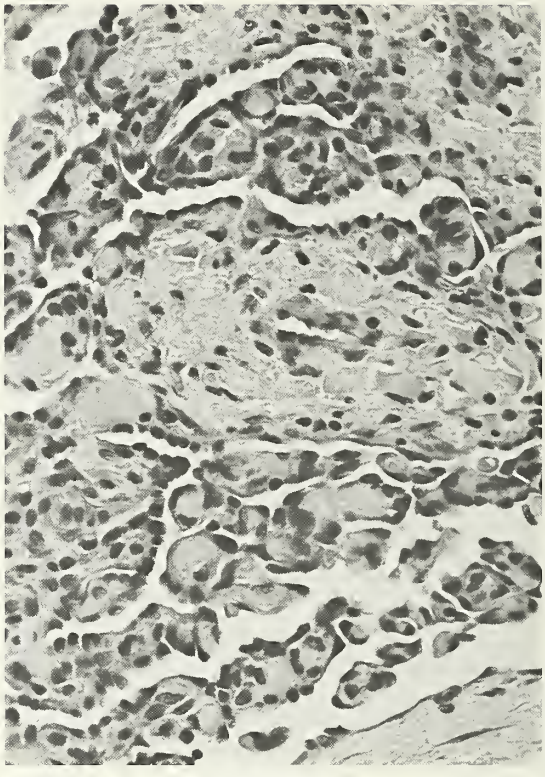


Figure 150
INTRAVASCULAR PAPILLARY ENDOTHELIAL HYPERPLASIA
High magnification of the previous illustration reveals the vascular nature of the interlumenal proliferation. X250.

CAVERNOUS HEMANGIOMA

Cavernous hemangiomas occur far less frequently in the upper respiratory tract. Their presenting signs and symptoms are like those of the capillary hemangioma. The turbinates, and not the septum, appear to be the sites of predilection. On occasion, the cavernous hemangioma may involve the bony structures of the paranasal sinuses. Microscopically, these lesions are composed of multiple large, thin walled, dilated, and blood-filled vascular spaces lined by a flattened endothelial layer.

When feasible, local resection leads to cure, but since some cavernous hemangiomas may manifest involvement of deeper structures, additional therapy may be required.

Venous hemangiomas, as described by Fu and Perzin, present in the nasal vestibule with external swelling. These tumors are broad-based and sessile. Thick walled venous channels with scattered arterioles, capillaries, and large feeding vessels make up their histologic appearance. The vessels often extend into the adjacent striated muscle and nasal cavity. Local resection appears an adequate form of management.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

SYNONYMS AND RELATED TERMS: Osler-Weber-Rendu disease.

Definition. The nasal mucous membranes are often involved by the autosomal dominant disorder, hereditary hemorrhagic telangiectasia (Harrison; Menefee et al.). In the skin and mucous membranes, the disorder presents in one of three forms: punctate; spider-like; and nodular. The lesion is one of a mechanical defect in the integrity of vessel walls. This makes them prone to rupture, either spontaneously or after minor trauma.

Clinical. Clinically, the disorder generally has a pattern of recurrent epistaxis, often beginning in early youth, with cutaneous lesions appearing in the second and third decades of life. Telangiectatic lesions are frequently found in the facial skin, especially at the nasal orifice and over the cheeks. In older patients, the clinical picture is not one of recurrent nasal bleeding, but rather of anemia.

Microscopic. The vascular lesions appear under the light microscopy as dilated blood channels composed only of an endothelial cell layer. Electron microscopic evaluation has identified the affected vessel as venules (Menefee et al.).

HEMANGIOMAS OF THE LARYNX

Two distinct clinical varieties of hemangioma occur in the larynx: the infantile and the adult (Bridger et al.; Littler; Ferguson). In the infantile forms, girls outnumber boys by at least 2 to 1. This is a marked contrast to the adult variety, where a majority have been men. The true incidence of laryngeal angioma in adults is probably very low, but has been spuriously enhanced by the inclusion of organizing hematomas.

Infantile Hemangioma of the Larynx

Clinical. In infants, usually in the earlier months of life, the tumors are usually sessile, diffuse lesions below the vocal cords, although they have been described in the supraglottic regions. They can increase in size rapidly, so that the patients have laryngeal obstruction within the first few months of life. Tracheostomy is often necessary before the patient reaches the age of 6 months. Fifty percent of patients have hemangiomas elsewhere, a feature that may be helpful in suggesting the correct diagnosis (Batsakis and Rice).

Gross. The lesions project into the airway, have a distinctive red blue color varying somewhat with the degree of vascular patency and depth beneath the mucosa, and are usually compressible. The lesions are localized to one side of the subglottis, usually the posterolateral portion. In the presence of these typical gross features, biopsy is probably not necessary and, indeed, is contraindicated because of the danger of fatal hemorrhage. A firm, noncompressible tumor may also be a cellular tumor with relatively few lumens in continuity with the general vascular bed, unlike the softer, compressible, cavernous variety.

Microscopic. Either capillary or cavernous forms may be present in the laryngeal hemangiomas (fig. 151) (Feuerstein).

Treatment. Five methods of treatment have been employed for subglottic hemangiomas: radiotherapy, steroids, injection of various chemicals, cryosurgery, and tracheostomy, followed by waiting for spontaneous regression. The first three methods are not regarded as effective and should not be used.

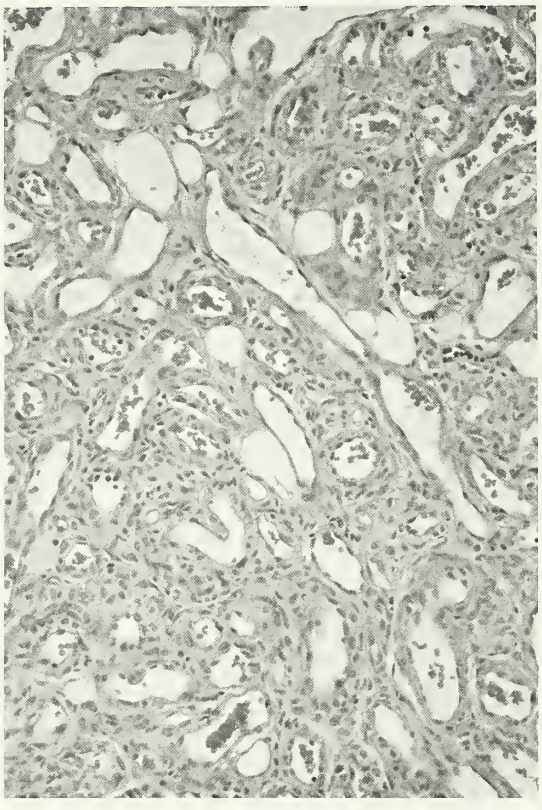


Figure 151
INFANTILE HEMANGIOMA OF THE LARYNX
In this infantile (embryonal) hemangioma of the larynx of a two month old, the vascular spaces are small with prominent endothelium. Some collapsed or immature vessels are seen focally in the intervascular space. X63.

Adult Hemangioma of the Larynx

The history of an adult laryngeal hemangioma may indicate that symptoms have been present for many years. The tumors are mostly rounded, projecting or pedunculated, purplish growths arising on or above the vocal cords. Occasionally, larger sessile tumors extend into the laryngopharynx.

As a rule, the only symptom is hoarseness; the tumors rarely progress to the point of causing respiratory embarrassment. Hemorrhage may occur spontaneously, but is more of a serious complication of operative interference. If at all possible, the hemangioma should be left alone with the initial management being conservative.

The so-called laryngeal granuloma or "contact" ulcer may be mistakenly diagnosed as a hemangioma of the adult larynx. This entity is discussed on page 17. Briefly, the laryngeal granuloma or "contact" ulcer is heavily male oriented, occurring in the middle or older age groups and often the patient has a long history of hoarseness and voice abuse. Chronic regurgitation of gastric contents is also a remote cause. The clinical location is most often the posterior vocal cord area, either unilateral or bilateral. The histology reveals a surface ulceration, but the underlying soft tissue histology will consist of a chronic vascular type granulation tissue that could be erroneously considered a form of hemangioma.

LYMPHANGIOMA

Lymphangiomas represent an anomalous development of lymphatic spaces (or combined blood vascular and lymphatic vessels) rather than a true neoplasm (figs. 152, 153). Involvement of the upper airway is usually secondary from lesions in the adjacent soft tissues.

Although there are reports of the lesions appearing in the gastrointestinal tract from the esophagus to the rectum, lymphangiomas primary in the hypopharynx and upper airway are nearly nonexistent, as judged by the literature. Lymphangiomyoma also has not been recorded in the supralaryngeal airway. A form of vallecular or pre-epiglottic cyst has been attributed to angiomatous malformation (blood or lymph vessels) (Ruben et al.).

A glomus tumor (glomangioma) of the nasal cavity is an extremely rare, or even questionable, lesion (Fu and Perzin).

Figure 152
LYMPHANGIOMA

A gross specimen of a cavernous lymphangioma of the neck in a 17 year old male who at birth presented with a soft neck mass that gradually grew until it had produced pressure on the respiratory and food pathways.

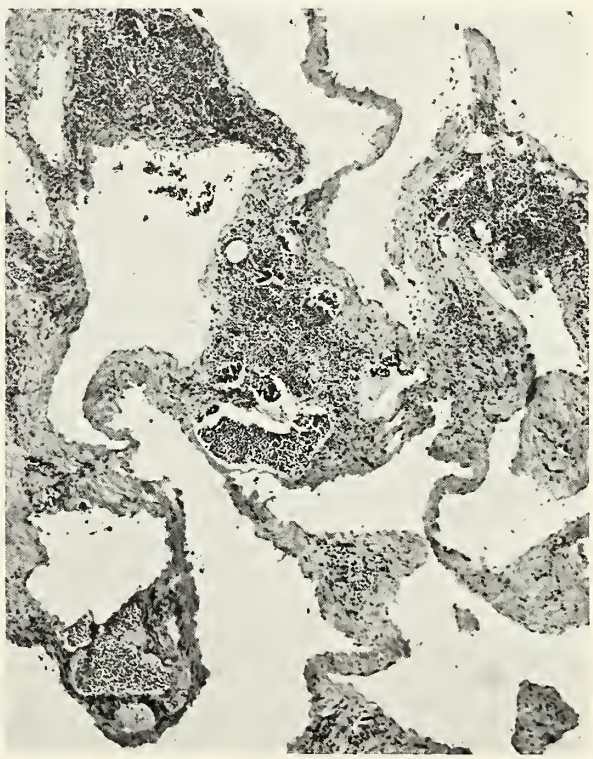


Figure 153
LYMPHANGIOMA

A large mass encroached upon the tracheal airway and esophagus in the neck of a newborn. Note the absence of blood in the cavernous spaces. X63.

ANGIOSARCOMA

SYNONYMS AND RELATED TERMS: Hemangiosarcoma; angioblastic sarcoma; hemangioendothelioma.

Definition. An angiosarcoma is a highly malignant neoplasm characterized by the formation of irregular anastomosing vascular channels lined by one or more layers of atypical dysplastic cells often of immature appearance. A malignant, histologic, intervascular, sarcomatous stroma may accompany the above pattern.

Sites of Tumor. Malignant endothelial neoplasms, angiosarcomas have a tendency to afflict the head and neck, particularly the scalp and facial soft tissues. Presentation within the structures of the upper airway, however, is most unusual. Testimony to this is the review by Pratt and Goodof, who could find only 15 patients with an angiosarcoma of the upper airway in a literature review that extended from 1892 to 1968. Even then, documentation was poor. Likewise, Bankaci and colleagues could find only 14 published cases where the angiosarcoma's origin was listed as the nasal cavity, paranasal sinuses, or nasopharynx. The maxillary antrum has been the most common area of involvement in the upper respiratory tract.

Incidence. Patients with angiosarcoma of the scalp and face are predominantly males who are elderly. Those with airway angiosarcomas tend to be younger and the sex ratio is more equalized.

Gross. Presentation may take one of three basic forms: ulcerating, diffuse superficial spreading, or nodular. They are usually blue or purple and often manifest intralesional hemorrhage. There is no capsule and there is a decided tendency for the tumors to spread through adjacent soft tissues for considerable distances.

Microscopic. At least two histologic grades of angiosarcoma exist: low- and high-grade or undifferentiated. The low-grade angiosarcoma may, on superficial examination, resemble a capillary hemangioma or even a pyogenic granuloma. However, the vascular spaces are lined by large, plump, atypical endothelial cells, the vascular spaces penetrate stroma, and there are papillary fronds of endothelial cells (fig. 154). Undifferentiated angiosarcomas are diffusely cellular and infiltrative (figs. 155, 156). Associated with both low- and high-grade angiosarcomas are proliferative vascular changes at a distance from the neoplasm.

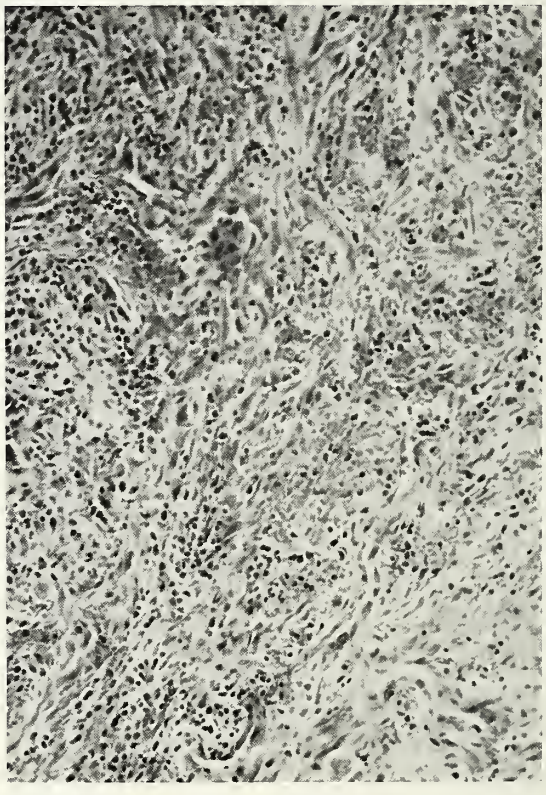


Figure 154
ANGIOSARCOMA
A low-grade angiosarcoma of the nasal vestibule characterized by vascular slits lined by plump dysplastic endothelial cells with areas of "tufting" of the lining neoplastic cells. X63.

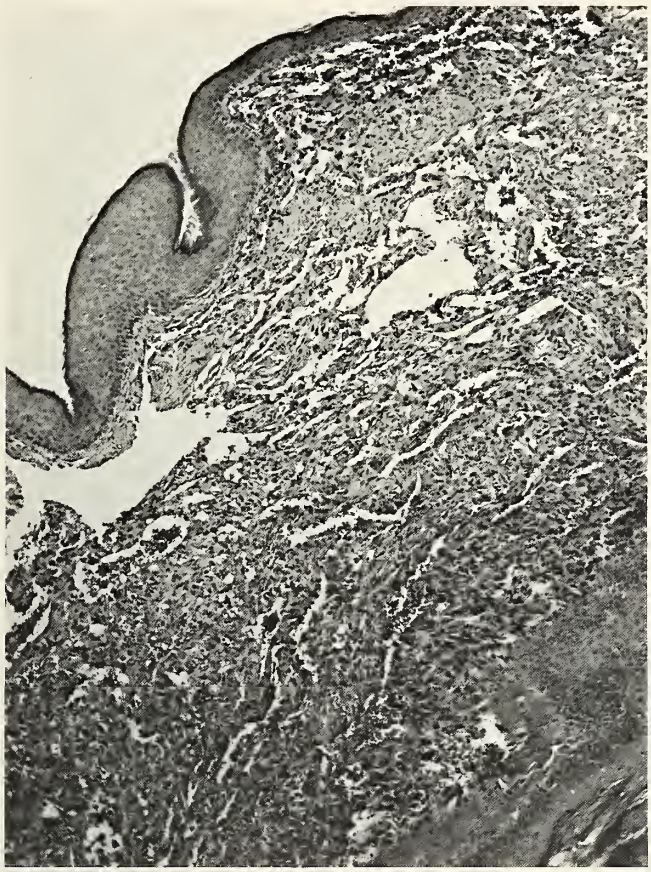


Figure 155
(Figures 155 and 156 are from the same patient)
ANGIOSARCOMA
A hemorrhagic mass involving the external ear and mastoid was diagnosed as a high-grade angiosarcoma because of the vascular space pattern lined by malignant cells, as well as a sarcomatous appearance of the intravascular tissue. X63.

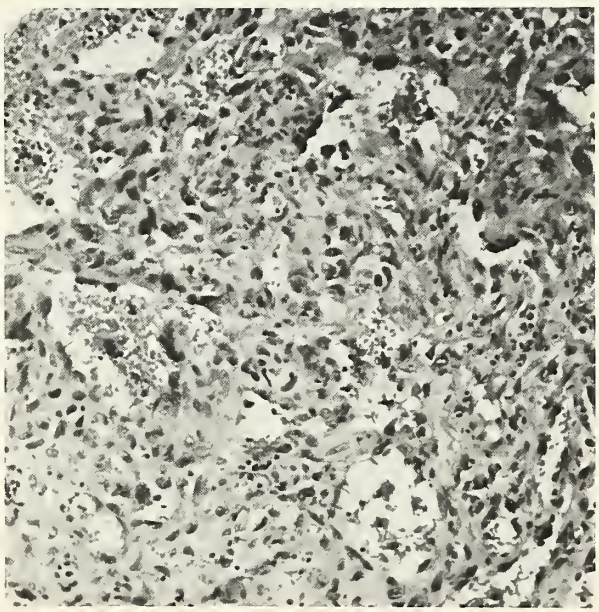
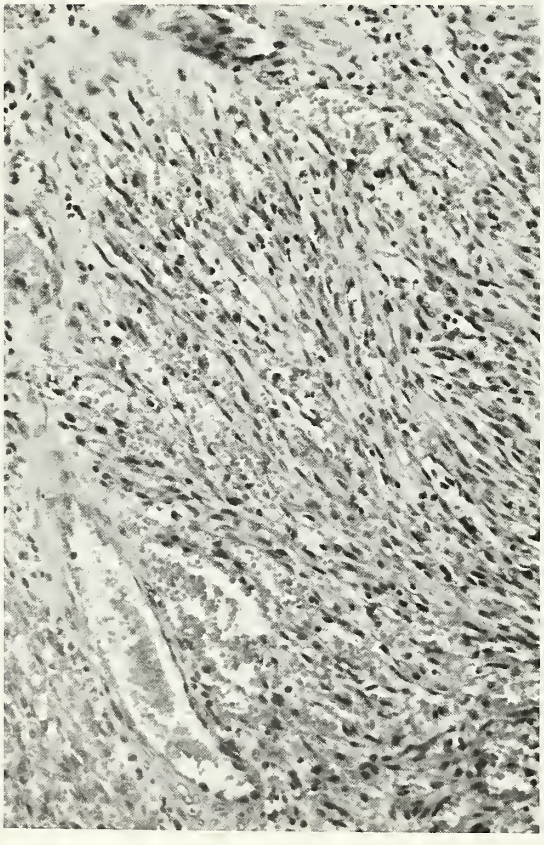


Figure 156
ANGIOSARCOMA
This higher magnification of figure 155 emphasizes the intra- and intervascular malignant cellular infiltrate. X160.

Differential Diagnosis. The differential diagnosis for low-grade angiosarcoma includes hemangioma, histiocytoid angioma, and pyogenic granuloma. The principal differential diagnosis for the high-grade tumors are poorly differentiated sarcomas, carcinomas, and melanomas.

Natural History. Angiosarcomas are therapy-resistant neoplasms. Half of the patients with angiosarcoma of the scalp and facial soft tissue are dead within five years of diagnosis. Although their number is small, there is a suggestion that angiosarcomas arising in the airway have a better prognosis. This observation, if accurate, may be related to an earlier diagnosis, younger age of patients, and a higher level of differentiation of the sarcoma (Batsakis et al.).



KAPOSI'S SARCOMA

The multifocal angiosarcoma, Kaposi's sarcoma (fig. 157), most often involves the skin, but visceral and lymph node involvement is not uncommon. Approximately 15 percent of patients with the disorder have a fatal visceral lesion. Primary tumors in the viscera, unassociated with any skin manifestations, have been found in African patients. Abramson and Simons have recorded the visceral involvements in the head and neck. The larynx and oropharynx are the most often involved sites. The classic Kaposi's sarcoma of the larynx has always been associated with cutaneous manifestations.

Recent reports have indicated almost epidemic numbers of cases of a progressive and quickly fatal form of Kaposi's sarcoma in the acquired immune deficiency syndrome (AIDS) (Gottlieb et al.; Hymes et al.). The neoplasm in these patients is characterized by a greater tendency to involve the skin and mucosa of the head and neck (Gnepp et al.) and cervical lymph nodes. Visceral involvement is more common than in the African and classic cases. Many patients have had oral mucosal lesions, particulary in the palate (Thomsen et al.) and tonsils. Accompanying infections by the organisms of Pneumocytis carinii, cytomegalovirus, and Crytococcus neoformans have supported the depression of immunologic function in these patients (Brennan and Durack).

Figure 157
KAPOSI'S SARCOMA
The histology of Kaposi's sarcoma is demonstrated by the fibrosarcomatous micromorphology with the incorporated intercellular slit-like spaces filled with erythrocytes. X160.

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HEMANGIOPERICYTOMA

Definition. For many years, since Stout and Murray separated it from other vascular neoplasms, the hemangiopericytoma has been a controversial lesion. Stout and Murray characterized the neoplasm as composed of capillaries surrounded by an accumulation of spindled or round to oval cells. They further demonstrated in tissue culture that the spindled or rounded cells came from Zimmermann's pericytes, and that the histogenesis of the neoplasm is similar and closely related to the glomus tumor.

The glomus tumor (glomangioma) arises from the neuromyoarterial glomera, has a distinctive organoid pattern, is associated with paroxysmal pain, may recur, and is usually benign. In the head and neck, the existence of a glomus tumor is very rare.

The hemangiopericytoma, in contrast, has no affiliation with glomera, is usually a large tumor, and is likely to exhibit a malignant biologic course.

The hemangiopericytoma has had various ultrastructural interpretations. Hahn and associates conclude that most of the cells are related to pericytes and a few possess features consistent with a smooth muscle origin. Battifora described cells that apparently represent transitions between the pericyte and endothelial cells.

Sites of Tumor and Frequency. Because the pericyte is found in capillaries and venules of practically all tissues, hemangiopericytomas have been reported from nearly all tissues of the body. The total incidence is low and the histopathologic appearance may be difficult to separate from other richly vascularized tumors. Both in biologic behavior and histopathologic features, the hemangiopericytomas may exhibit extraordinary variation. Many of the "variations" may be due to the inclusion of tumors that have been misdiagnosed as hemangiopericytomas.

In overall frequency, the number of reported and documented hemangiopericytomas are almost equally divided between the external soft tissues and the internal tissues and bone. In the AFIP-OTR series of 106 hemangiopericytomas, the soft tissues of the head and neck were the third most frequently cited primary sites, behind the lower extremities (35 percent) and the retroperitoneum and pelvis (24 percent) (Enzinger and Smith).

The region of the head and neck accounts for approximately one fourth of all reported cases in both children and adults. In 98 lesions involving the external soft tissues, Stout reported 24 as presenting in the head and neck (scalp, face, auricle of ear, and neck). Eleven of 31 hemangiopericytomas in childhood were from this region and, in fact, the head and neck is the favorite site in this age group (Kauffman and Stout).

In the upper airway, hemangiopericytoma has been reported 17 times prior to 1976 (Cantrell et al.). To this, Compagno and Hyams added an additional 23 intranasal tumors. We include their patients even though they regarded the lesions as "a peculiar form of vascular neoplasm within the histologic spectrum of traditional hemangiopericytoma." The larynx is an extremely unusual site for a hemangiopericytoma (Ferlito).

Incidence. In the nasal cavity and paranasal sinuses, the tumor has presented over a wide age range, from newborn to 80 years. Most often they occur in the sixth and seventh decades of life. There is no significant sex predilection.

Gross. When in the nasal cavity, these lesions often originate in a paranasal sinus and extend into the nasal cavity secondarily.

While there is no typical gross appearance, the tumors most often have been described as red-tan to gray-tan, obstructive, and polypoid masses high in the nasal cavity. They tend to bleed easily on manipulation. Eneroth and associates caution against this complication when biopsy is performed.

Microscopic. The hemangiopericytoma is a circumscribed or pseudoencapsulated vascular neoplasm characteristically composed of tightly packed cells about thin walled endothelial lined spaces that vary from gaping, sinusoidal-like channels to capillaries (figs. 158, 159). An associated dilatation of veins in the vicinity of the tumor may be seen.

The tumor cells possess an oval or elongated nucleus and an indistinct cytoplasm. Masson trichrome and phosphotungstic acid hematoxylin (PTAH) stains fail to demonstrate intercellular myofibrils.

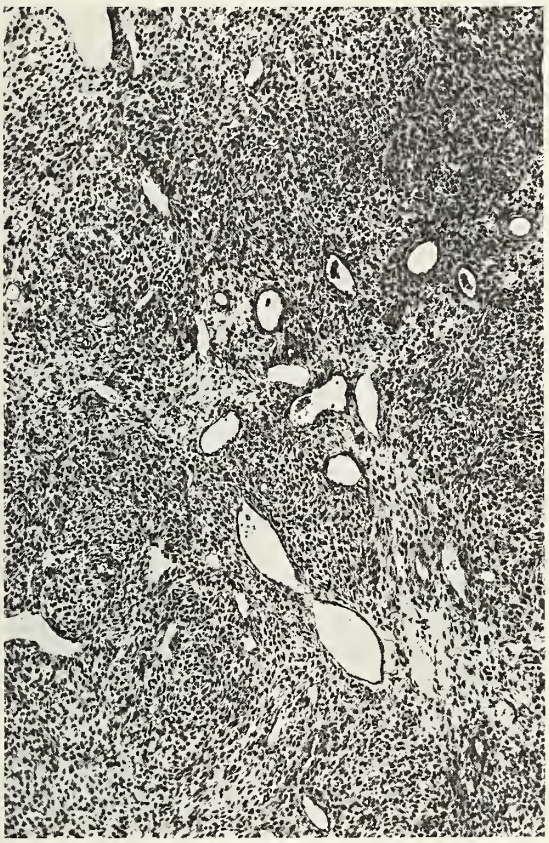

Figure 158
HEMANGIOPERICYTOMA
A hemangiopericytoma-like lesion of the nasal cavity in a middle aged adult depicts increased ratio of neoplasm to vascular structures, which is the usual situation. X50. (Fig. 1 from Compagno, J. and Hyams, V.J. Hemangiopericytoma-like intranasal tumors. Am. J. Clin. Pathol. 66:672-683, 1976.)

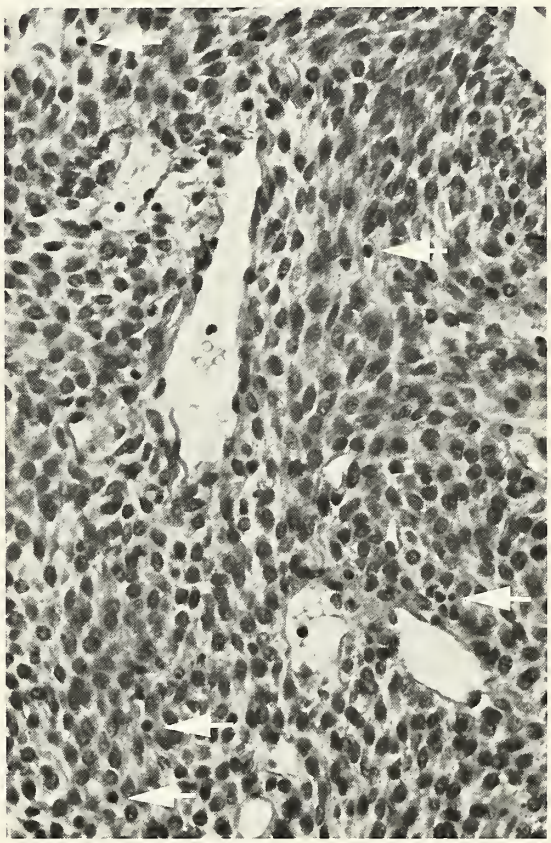

Figure 159
HEMANGIOPERICYTOMA
In this higher magnification of a hemangiopericytoma-like neoplasm of the sinonasal tract, the vascular element is felt to be histologically benign. The spindle cell element is uniform and mast cells are present (arrows). X225. (Fig. 5 from Compagno, J. and Hyams, V.J. Hemangiopericytoma-like intranasal tumors. Am. J. Clin. Pathol. 66:672-683, 1976.)

In contrast to the concentric organoid perivascular arrangement of the glomus tumor, the organization of the cells in a hemangiopericytoma is more haphazard. The cellular conformation, however, is relatively uniform.

In some tumors, spindle-shaped cells predominate, but these cells are not arranged in a fascicular or bundle pattern as seen in synovial sarcomas or fibrosarcomas. An occasional spindle cell pattern may approach the appearance of a fibrous histiocytoma.

The vascular pattern is one of a continuously ramifying system. Large channels extend from the pericapsular tissue into the tumor in a radial fashion. These branch into dilated sinusoidal-like spaces or into vessels of precapillary or capillary size. Vessels with a thick muscular coat are unusual. The vessels, regardless of their size, are thin walled and lined by a single layer of endothelium. These vessels are often indented by a knob-like protrusion of tumor cells.

Reticulum preparations (Wilder or Snook) demonstrate a basement membrane separating the vascular spaces from the surrounding reticulum meshwork. Reticulin and collagen fibers also enmesh the tumor cells outside the vascular channels. This pattern is not only variable from tumor to tumor, but also within different areas of a given tumor.

Fibrosis is nearly always present and may be diffuse, localized, or primarily perivascular. Osseous and cartilaginous metaplasia is noted on occasion. This microscopic characteristic of cartilaginous tissue inclusion is also shared with the embryonal chondrosarcoma which is sometimes misdiagnosed as hemangiopericytoma. An innervation so characteristic of the glomus tumor is absent.

Focal infarction may occur, sometimes associated with thrombotic occlusion of a large vessel. Hemorrhage is an accompaniment of these changes, as is an increase in the amount of interstitial mucoid material. Necrosis, hemorrhage, and thrombosis are seen chiefly in cellular and rapidly growing neoplasms. Peripheral satellitosis and vascular invasion may be seen.

A distinction between benign and malignant hemangiopericytoma is often difficult (fig. 160). Certain features, however, assist in that effort.

In the intranasal tumors, the following features point to a benign course: absence of or minimal mitotic activity; clear distinction

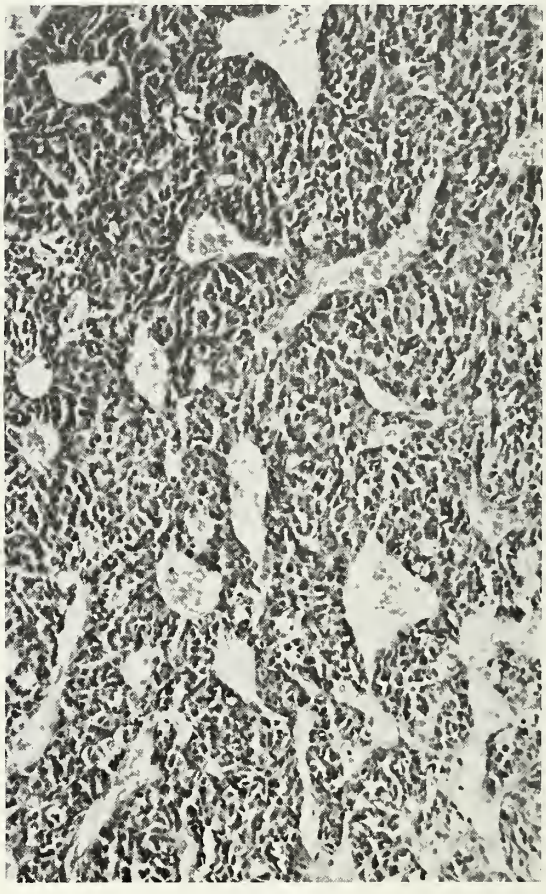

Figure 160
HEMANGIOPERICYTOMA
A malignant hemangiopericytoma of the nasopharynx reveals a more dysplastic hyperchromatic neoplastic cell, but retains the overall general architecture of the neoplasm. X63.

of normal vessels from tumor cells (usually by a thin connective tissue sheath); uniform spindle cells with little or no overlapping of cell borders; absence of necrosis; and the presence of scattered mast cells.

Survival is said to be less favorable for those tumors without a lymphocytic infiltrate, few vascular spaces, and little desmoplasia.

A malignant course may be expected for those tumors with one or more mitotic figures per 10 high power fields and slight cellular anaplasia or one or more mitotic figures per 20 high power fields and moderate cellular anaplasia (McMaster et al.).

Natural History. Unpredictability has characterized the biologic behavior of all hemangiopericytomas. A metastatic rate of approximately 50 percent has been repeatedly indicated (McMaster et al.; O'Brien and Brasfield). Recurrence rates, even without eventual metastases, are also high. It should be noted that metastases may occur after a prolonged tumor-free interval.

In some series, anatomic distribution has had a bearing on malignancy, but this has not been completely substantiated (Batsakis and Rice).

In the upper respiratory tract, after combining the survey by Cantrell and associates and Compagno and Hyams (42 patients), the tumors appear to deviate from the course followed by their counterparts elsewhere. Recurrence and/or persistence of tumor prevailed in six patients (14 percent) and metastases occurred in three patients (7 percent).

Hemangiopericytomas of the sinonasal cavity, as a group, tend to be lesions of local consequence and appear to be effectively controlled with adequate local excision.

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TUMORS OF MUSCLE

LEIOMYOMA

Tumors of smooth muscle origin rank among the least frequent of all nonepithelial lesions of the head and neck. Because of a paucity of smooth muscle in most areas of the head and neck, the smooth muscle of the walls of blood vessels has been proposed as the progenitor tissue for most of the smooth muscle tumors. Many of the benign forms may, in fact, be hamartomatous.

Sites of Tumors. Compared with the superficial soft tissues, the upper aerodigestive tracts are unusual sites for smooth muscle neoplasms. Also, in the majority of these areas, they are regarded as being of vascular derivation, hence the alternated designation angioleiomyoma and angioleiomyosarcoma. In the reported cases in the upper respiratory tract, however, leiomyosarcomas outnumber leiomyomas. Fu and Perzin (1975) added six examples to six previously reported patients with leiomyosarcomas of the sinonasal tract and nasopharynx, while Mindell and associates added two cases together with a review of relevant published literature.

Kleinsasser and Glanz, in their review of myogenic tumors of the larynx, found 15 acceptable examples of leiomyoma and 8 leiomyosarcomas. In the larynx, the majority are supraglottic and appear to originate in the vestibular folds. Large tumors distend the aryepiglottic fold and expand into the pyriform sinus or protrude from the ventricle. The trachea (lower third) has been a reported location for smooth muscle tumors (Sanders and Carnes).

Leiomyomas have been reported in children, but more often they occur in adults of all ages. Except for vascular leiomyomas of the skin, there is an overall male predominance of 2 to 1.

Gross. The typical leiomyoma of the airway (fig. 161) is a slowly enlarging, relatively discrete, and usually solitary submucosal mass. They are usually sessile, but may assume a polypoid configuration on a small pedicle. The size of the tumors may range from a few millimeters to several centimeters, depending on their vascularity, which also influences their color, gray-pink to red. Necrosis and ulceration are distinctly uncommon. Although 80 percent of subcutaneous leiomyomas are said to be painful and/or tender, these findings are very unusual in the submucosal tumors.

Microscopic. The microscopic appearance of leiomyoma will vary in accordance with the degree of vascularity of the tumor, but all contain typical well differentiated smooth muscle cells. Mitoses are not found and nuclear atypia is absent or minimal. The vascular leiomyoma (angioleiomyoma) has a very characteristic structure (fig. 162). Blood vessels with thick walls consisting of leiomyocytes are seen. Nodular and whorled cellular patterns occur in addition to a sponge-like structure which is rich in fibers but contains few nuclei (figs. 163, 164). Masson's trichrome stain will demonstrate bright red intracytoplasmic fibrils. The ultrastructural appearance of a benign, smooth muscle cell is characteristic. Individual cells are usually invested by a basement membrane and variable numbers of pinocytotic vesicles can be identified in close proximity to the plasma membrane. The cytoplasm contains a heavy concentration of microfilaments along with

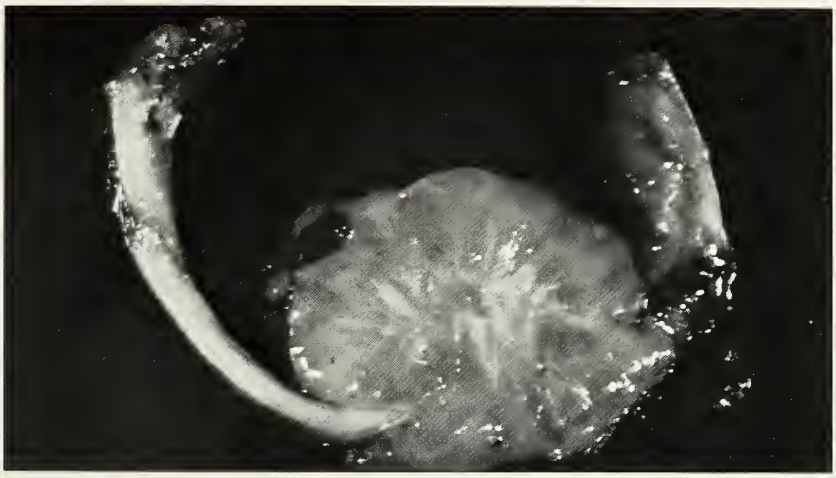

Figure 161
LEIOMYOMA
A leiomyoma of the trachea.

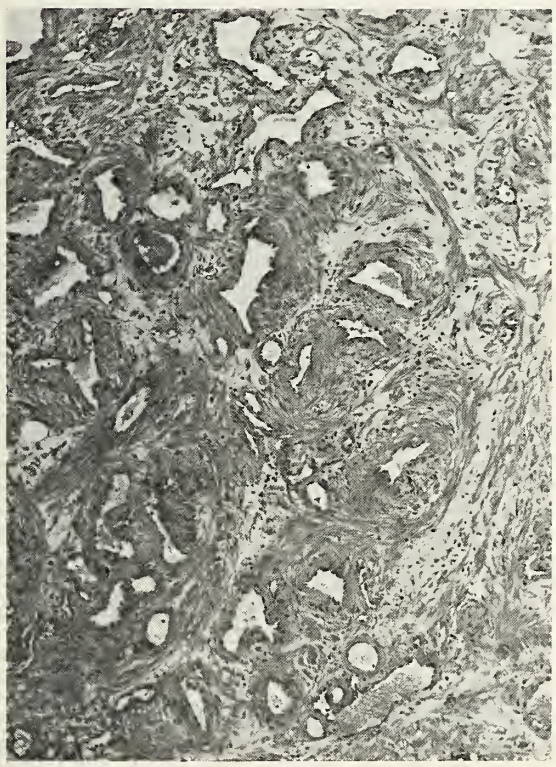

Figure 162
LEIOMYOMA
This vascular leiomyoma (angioleiomyoma) of the nasopharynx consists of numerous benign, endothelial-lined, vascular spaces with thick walls consisting of leiomyocytes. X63.

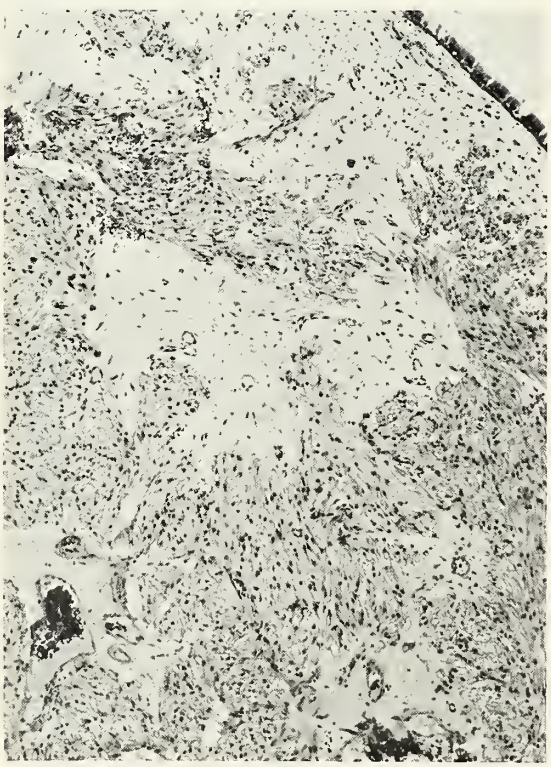

Figure 163
(Figures 163 and 164 are from the same patient)
LEIOMYOMA
This leiomyoma of the nasal cavity consists of uniform spindle cells arranged in fascicles alternating with myxomatous stroma and prominent vascular structures. X63.

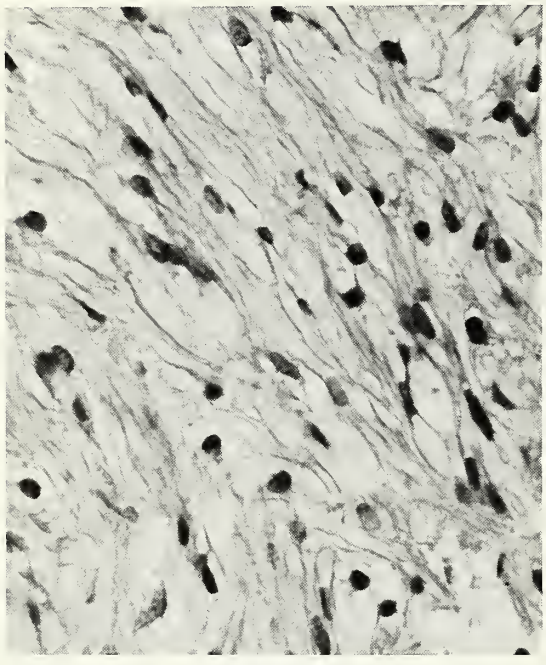

Figure 164
LEIOMYOMA
Higher magnification of the previous illustration emphasizes the spindle cell morphology, the uniformity of the cells and their nucleus. X400.

numerous electron dense bodies and marginal dense plaques, the latter just beneath and probably associated with the cell membrane. The dense bodies and plaques are the most distinctive ultrastructural findings in smooth muscle.

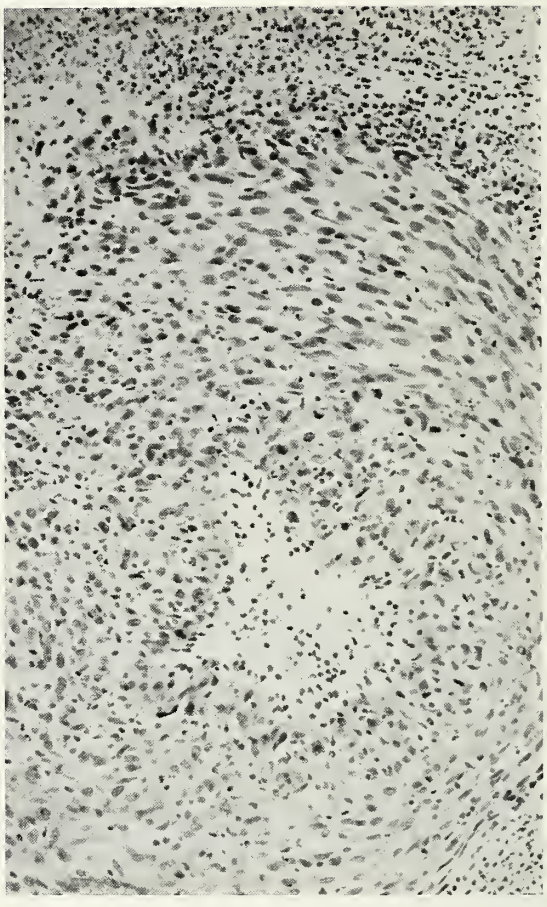

Figure 165
LEIOMYOSARCOMA
Note the arrangement of pleomorphic spindle cells around a vascular lumen. X160.

LEIOMYOSARCOMA

Leiomyosarcomas do not differ significantly in sites of involvement, age of patients, or sex preference from leiomyomas of the sinonasal tract and the remainder of the upper airway.

Gross. Their size is always larger than the leiomyoma and may be 5 or 6 cm at the time of diagnosis. They are usually characterized as gray-red, hemorrhagic, and necrotic neoplasms which invade adjacent tissue. They present with a sessile or polypoid configuration. Ulceration and necrosis are common for the airway tumors, but less for those in the soft tissue and digestive portions of the head and neck.

Microscopic. Leiomyosarcomas are more cellular, always have anaplastic cells, very often manifest at least some bizarre cells, and may not manifest easily recognizable myofibrils (fig. 165). Mitoses are always found, sometimes in considerable number. Typically, the neoplasm is composed of bundles of

spindle-shaped cells. Often there will be nuclear palisading of elongated, blunt ended nuclei. On cross section, the nuclei are often surrounded by a clear halo. With hematoxylin and eosin stains, the cytoplasm has an eosinophilic, fibrillary appearance. With Masson's trichrome, there are red intracytoplasmic fibrils. The number of these cells, however, is quite variable. Laidlow's stain demonstrated reticulin fibers either parallel to muscle bundles or surrounding individual cells.

Natural History. Leiomyomas should not recur after adequate surgical removal. The majority of the laryngeal leiomyomas can be removed endoscopically (Kleinsasser and Glanz). Leiomyosarcomas, however, are typically characterized by a high incidence of recurrence. This may be due in great measure to the manner with which primary surgery was performed and to the local extent of the neoplasm. In the sinonasal tract and nasopharynx, these recurrences often become uncontrollable and manifest extensive local infiltration. In all areas, the recurrent neoplasm is larger and generally fixed to contiguous soft tissue structures and bone.

Metastases are principally hematogenous and to the lungs. Widespread hematogenous dissemination also occurs. Lymph node metastases occur in approximately 10 percent of patients.

BIZARRE LEIOMYOMA

SYNONYMS AND RELATED TERMS: Leiomyoblastoma; epithelioid leiomyoma.

The epithelial "bizarre" leiomyoma or leiomyoblastoma in the upper airway (fig. 166) has to be regarded as a medical curiosity. The AFIP-OTR data contain three examples: two in the nasal cavity and one in the pterygomaxillary fossa.

RHABDOMYOMA

Definition. Rhabdomyoma is a benign neoplasm consisting usually of polygonal, frequently vacuolated (glycogen containing) cells having a finely granular, deeply acidophilic cytoplasm. Cross striations are usually seen within the tumor cells.

Mesenchymal tumors forming skeletal muscle have a predilection for the head and neck. The vast majority of these are malignant — rhabdomyosarcomas. Much more rare are benign tumors of skeletal muscle origin — rhabdomyomas. Two forms of rhabdomyoma are recognized; an adult type and a less frequent fetal type (Batsakis et al.).

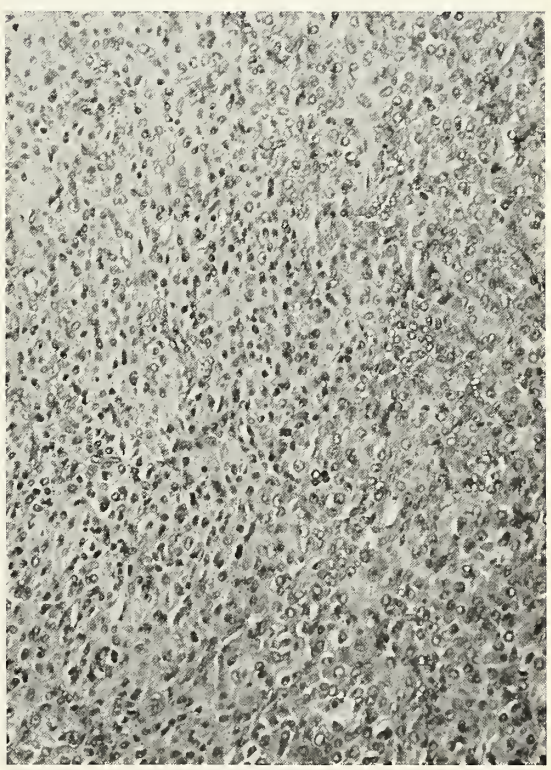

Figure 166
BIZARRE LEIOMYOMA
A bizarre leiomyoma of the tracheal has rounded or polygonal cells with acidophilic cytoplasm and an occasional space partly surrounding a nucleus. No mitotic figures are prominent. X160.

Adult Rhabdomyoma

Adult rhabdomyoma is a term used for two classes of tumors: cardiac and extracardiac. The cardiac type occurs more frequently and even though it is most often encountered in infants and children, it has been included in the adult rhabdomyosarcoma class in contrast to the fetal rhabdomyoma, which will be discussed later. This cardiac rhabdomyoma is considered to arise from primitive cardiac muscle and is a malformation or hamartoma, possibly related to localized glycogen storage disease.

Extracardiac adult rhabdomyomas, like their fetal extracardiac counterparts, display a definite predilection for the head and neck. The tumors present over a wide age range, but most patients are over 35 years of age. Multifocal tumors are possible, but unusual (Fu and Perzin, 1976).

Sites of Tumor. Unlike rhabdomyosarcomas which may arise in areas with sparse or nondemonstrable skeletal muscle, adult rhabdomyomas always arise in sites where there is skeletal muscle. In the oral cavity, the tongue and the floor of the mouth are favored sites. Pharyngeal sites have been recorded from the base of the skull to the pyriform fossa. In the larynx, the tumors may arise in any portion, but there is a slightly higher incidence in the vocal cords (Ferlito and Frugoni). The nasopharynx is perhaps the least frequent location.

Gross. The tumors are solitary, lobulated, and apparently well circumscribed lesions that are fleshy and yellow to red-brown. The size varies from a few centimeters to more than 10 cm.

Microscopic. Microscopic examination reveals large round to oval cells with pale, faintly granular eosinophilic cytoplasm (figs. 167, 168). Many cells contain large cytoplasmic vacuoles, mainly at the periphery of the cell. Nuclei are bland and also tend to be located at the periphery. A so-called spider cell appearance is conveyed when the cell's nucleus is centrally placed and surrounded by vacuoles in a threadlike structure. A few of the cells show definite cross striations (fig. 169) and some cells contain a collection of crystal-like particles in a haphazard arrangement.

Positive PAS reactions that disappear after diastase digestion establish that the substance found within the vacuoles of the cytoplasm of the cells is probably glycogen.

Ultrastructural studies show that the tumors reproduce striated muscle myofibrillar structure, but with a disturbance of the regular myofibril pattern. All tumors have Z bands and attached thin filament-forming I bands. The Z lines are manifested under light microscopy as a component of ill defined striations and as small crystals (Wyatt et al.).

Natural History. The tumors have never been associated with malignant transformation. Recurrences are always attributable to incomplete removal.

Fetal Rhabdomyoma

The fetal rhabdomyoma, while not limited to children, is a lesion usually becoming clinically apparent shortly after birth. It may be hamartomatous (Dehner et al.).

Site of Tumor. The tumor is nearly always solitary and is usually subcutaneous. It has not been described as occurring in the upper respiratory tract, but has a tendency to present in the postauricular area, and because of this proximity to the external ear it is included in this discussion. It is more likely to occur in girls.

Gross. Fetal rhabdomyomas appear moderately well circumscribed and some may

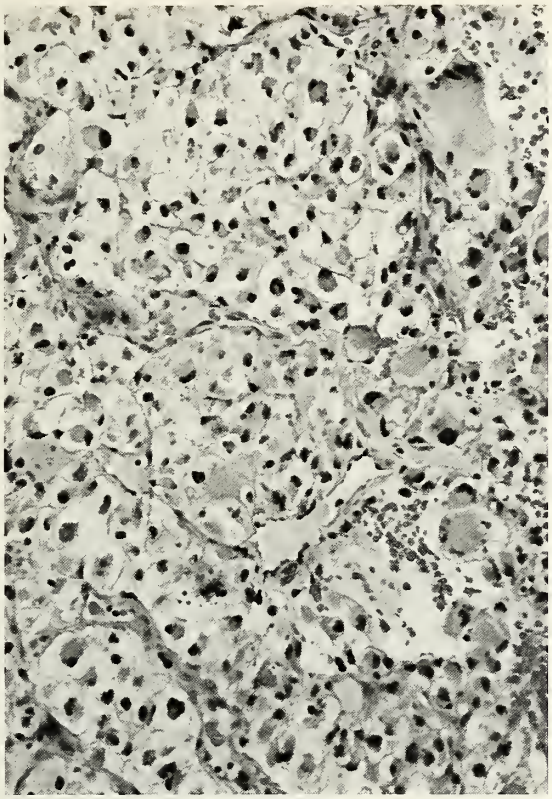

Figure 167
(Figures 167 and 168 are from the same patient)
RHABDOMYOMA
A rhabdomyoma of the larynx consists of large round to oval cells with a pale, faintly granular, eosinophilic cytoplasm. Many cells contain large cytoplasmic vacuoles, mainly at the periphery. X160.

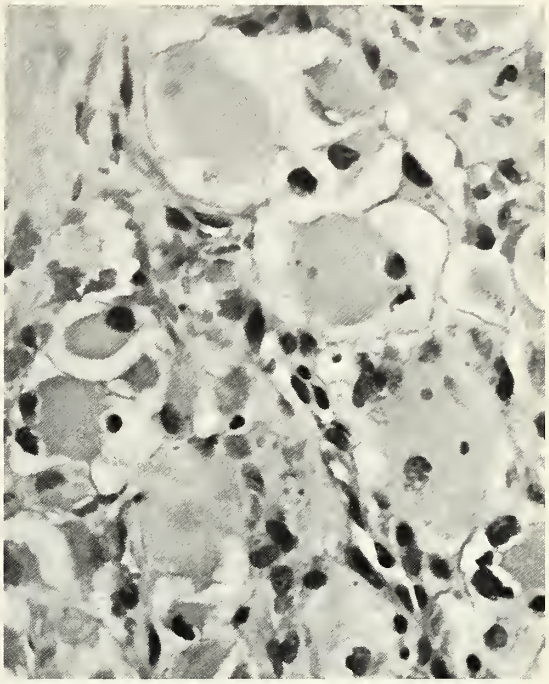

Figure 168
RHABDOMYOMA
Note the spider cell appearance which is conveyed when the cell nucleus is centrally placed and surrounded by vacuoles in a thread-like structure. X400.

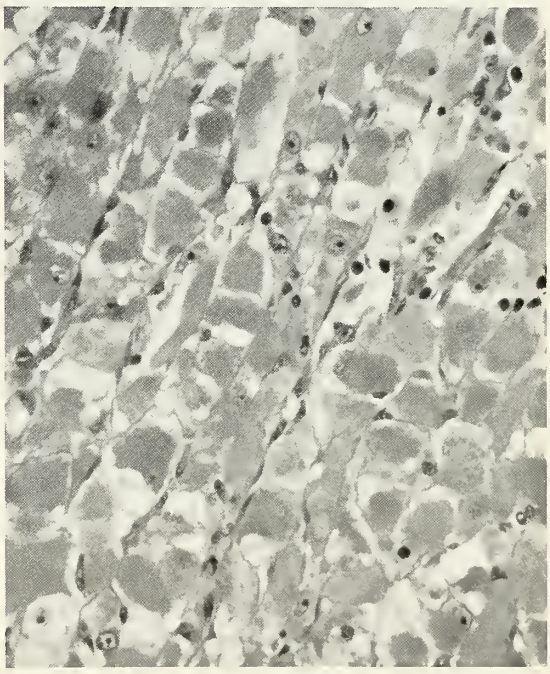

Figure 169
RHABDOMYOMA
This rhabdomyoma of the larynx from a 17 year old male has mature tumor muscle cells with rare cross striations. X160.

give the impression of being encapsulated. Their size has ranged from 1 to 8 cm. They are not tender and they are fluctuant or rubbery.

Microscopic. The fetal rhabdomyoma is composed of two basic cellular elements set in an edematous, vacuolated matrix that is rich in acid mucopolysaccharides (figs. 170, 171). The cells include immature skeletal muscle fibers in various stages of differentiation, and also undifferentiated mesenchymal cells. The relative proportion of these cells varies in different parts of the tumor, but there is a tendency for maturation to proceed from the center of the tumor to the periphery. The muscle fibers resemble the striated muscle in the 6 to 10 week stage of embryonic development. Myofibrils are usually well developed, but cross striations are scarce. Microscopically, no capsule is present and, while margins may be blurred, true infiltration into adjacent tissues is never prominent. Necrosis, mitoses, and atypia are not found (Dahl et al.).

Ultrastructurally, the tumor is composed of cells demonstrating myoblastic or myotubular differentiation (Walter and Guerbaoui).

Treatment. Local excision is curative.

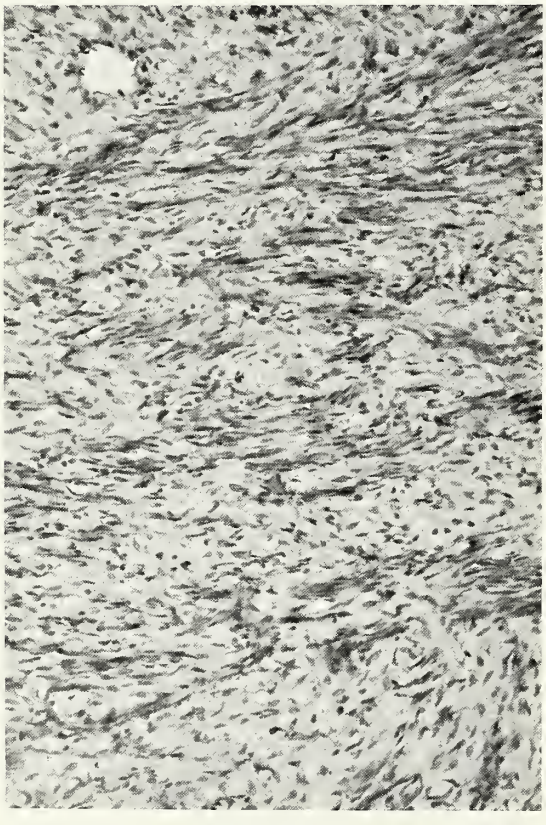

Figure 170
(Figures 170 and 171 are from the same patient)
FETAL RHABDOMYOMA
A posterior auricular mass in a two year old girl revealed an edematous vacuolated matrix containing immature, but histologically benign, skeletal muscles. X160.

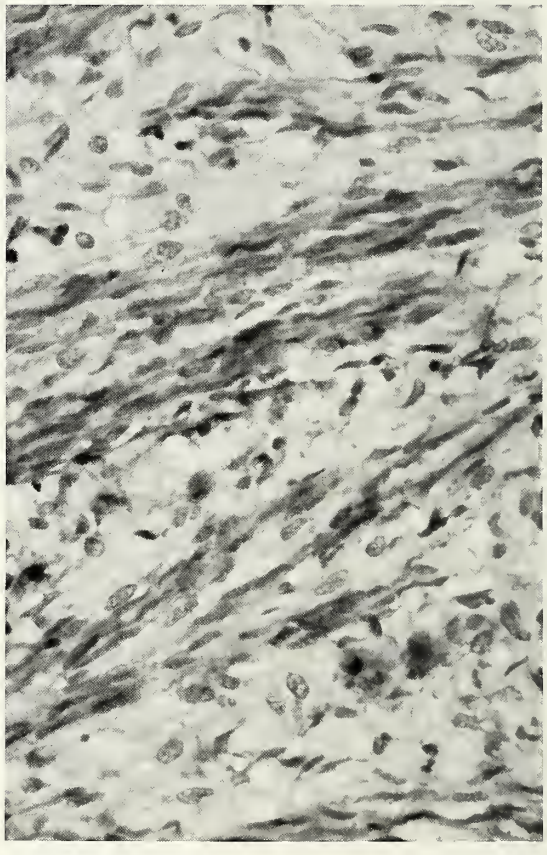

Figure 171
FETAL RHABDOMYOMA
A higher magnification of the previous illustration. X400.

RHABDOMYOSARCOMA

Definition. Rhabdomyosarcoma is a highly malignant tumor of rhabdomyoblasts in varying stages of differentiation with or without intracellular myofibrils or cross striations.

Incidence. This tumor is the most common soft tissue malignancy in patients under the age of 15 years and is the most common sarcoma in the head and neck. Rhabdomyosarcoma of the head and neck is principally a disease of the first decade and a half of life. Nearly 80 percent of diagnoses are made in children under the age of 12 years. Its incidence among caucasians is higher than among blacks. No specific familial disease has been associated with an increased risk and the concordance rate in siblings is considerably lower than that for a number of other childhood malignancies (Batsakis et al.). Jaffe and associates, in analyzing 40 cases of rhabdomyosarcoma of the middle ear and mastoid, reported the typical age range from 1 to 12 years (average 4.4 years) with only a rare case recorded in adults. Sex incidence and site of involvement were equal.

Sites of Tumor, Clinical Data, and Gross. Anatomic distribution within the head and neck for this malignancy as defined by Dito and Batsakis in 1962 has been repeatedly confirmed. The orbit and eyelids remain an area of predilection, followed by the aerodigestive tracts; soft tissues of face and neck; air cavities, such as the middle ear, mastoid, sinuses, larynx; and parasalivary gland sites.

Rhabdomyosarcoma of the nasal cavity, nasopharynx, and paranasal sinuses presents as a mass, nasal bleeding, obstruction, ear pain, poor vision, and at times proptosis. The nasal cavity is almost always involved whether the lesion is primary or from adjacent sinuses. Nearly every sinus has been described as the site of origin, as well as the nasopharynx. The nasopharynx ranks second only to the orbit as the most frequent site of origin. Between 15 and 20 percent of the head and neck rhabdomyosarcomas involve the nasopharynx.

Tumors in the nasal vestibule and ala nasi have a tendency to be small (less than 2 cm). Those in the nasal passages and nasopharynx have generally attained a relatively large size when discovered. They partially or completely occlude the lumen of the affected passage. Approximately one-fourth of these neoplasms will assume a botryoid configuration. These are grape-like and polypoid masses, often appearing translucent, not unlike a nasal polyp. Others are solitary, smooth surfaced, and polypoid or dumbbell shaped. Both botryoid and the red-gray, firm, polypoid tumors often manifest an irregular extension into adjacent structures.

In the larynx, there is a tendency for origin in the glottis, where the tumors tend to be bulky, sessile, or pedunculated masses which may be covered by an ulcerated mucosa. It is also evident that laryngeal rhabdomyosarcomas occur over a wider age range, with patients' ages ranging from newborn to 76 years (Canalis et al.).

The site of origin of rhabdomyosarcoma in the temporal bone is difficult to determine because, in most cases, both the middle ear and external auditory canal are involved by tumor at the time of diagnosis. One patient in which the neoplasm originated from the external auricle is found in the AFIP-OTR material. A prominent clinical feature is the seemingly innocuous early symptomatology. A common first complaint is aural discharge, often bloody, and then the presentation of a "polyp" in the external auditory canal. Rarely is the occurrence of a mass in the temporal bone or metastatic disease an early symptom or sign. Serious signs, such as

cranial palsy (primarily the seventh nerve) are usually not long in developing. Early in the disease process, the clinical and even histologic diagnosis has often been chronic otitis media. Grossly, the neoplasm may be a dark red, lobulated, fungating mass of varying consistency or, when in the confines of the temporal bone, the infiltrating tumor is more likely to have a necrotic hemorrhagic appearance.

Microscopic. Rhabdomyosarcomas, in a sense, recapitulate the embryogenesis of skeletal muscle, but in a disorganized manner. The malignant myoblast may assume, in accordance to its resemblance to developing muscle, several forms: small round (primitive mesenchymal) cells, a mesenchymal syncytium-like cell, a tubular form, or racquet, strap, and spider-shaped cells. Clearly, all these cells do not contain cross striations, and their absence or the inability of the examiner to find them does not exclude the diagnosis.

Rhabdomyosarcomas, regardless of site, fall into three major histologic subtypes: embryonal, alveolar, and pleomorphic, or combinations of these types. The botryoid form should not be considered a histologic

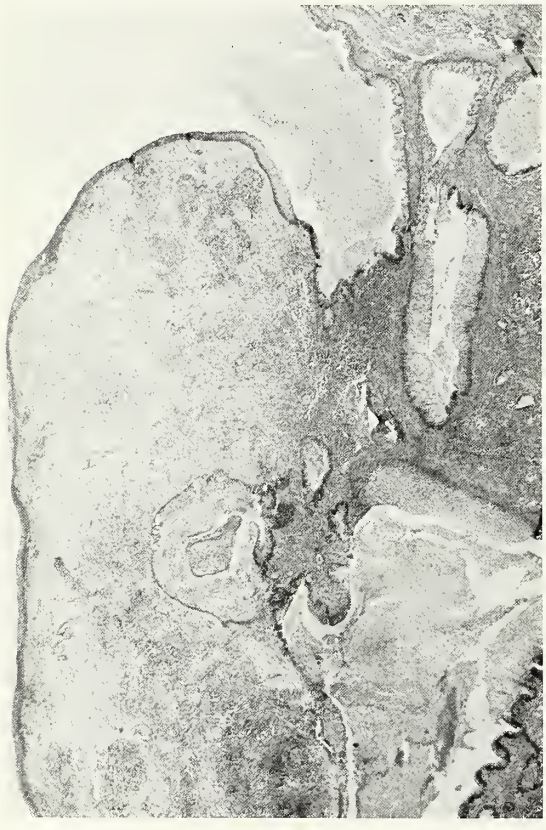

Figure 172
RHABDOMYOSARCOMA
A polypoid mass of the nasal cavity in a seven year old boy represents a juvenile rhabdomyosarcoma. This may be referred to as a "sarcoma botryoid" type. X25.

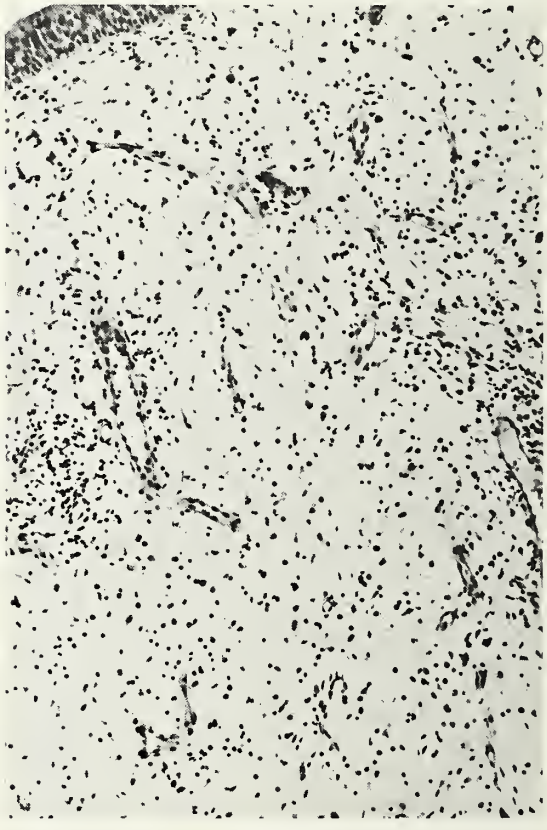

Figure 173
RHABDOMYOSARCOMA
This polypoid juvenile rhabdomyosarcoma of the sinonasal tract emphasizes the myxomatous histology that sometimes is confused with an inflammatory polyp of the anatomic area. X125.

type, since it refers to a gross configuration. Likewise, "sarcoma botryoid" is an inappropriate microscopic designation. In the instance of rhabdomyosarcoma, virtually all botryoid rhabdomyosarcomas are of the embryonal type. The pleomorphic rhabdomyosarcoma is a rare type in the head and neck area. Some classifications designate this type as adult rhabdomyosarcoma and consider the remaining classifications (embryonal and alveolar) as juvenile rhabdomyosarcoma.

Histologically, the embryonal form is the most commonly occurring rhabdomyosarcoma in the head and neck. Of the three major subclasses of rhabdomyosarcoma (pleomorphic, embryonal, and alveolar), only the embryonal form has an unequivocal resemblance to developing normal fetal muscle. Light microscopic observations that the alveolar rhabdomyosarcoma corresponds to the myotube stage of muscle differentiation have been challenged by ultrastructural examination. The pleomorphic sarcoma does not resemble any stage of embryonic muscle development.

Embryonal rhabdomyosarcoma. The embryonal rhabdomyosarcoma (figs. 172-175) contains both round and spindle neoplastic

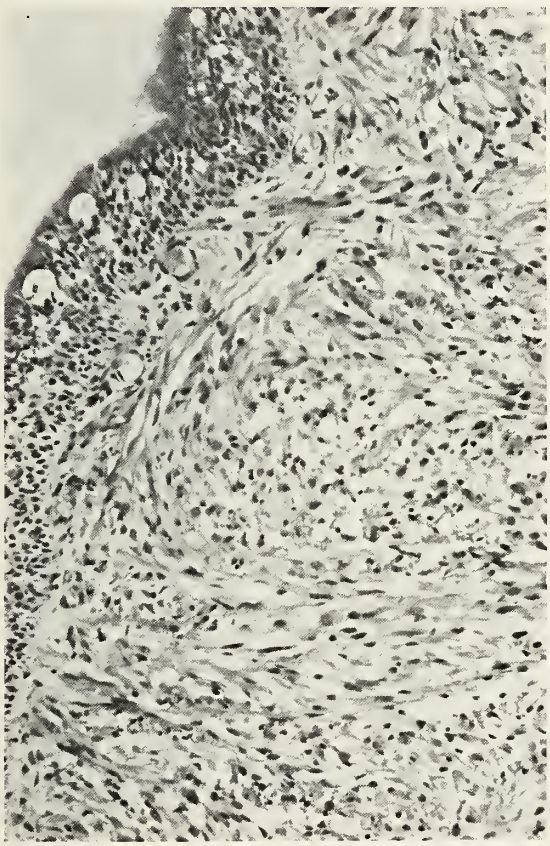

Figure 174
RHABDOMYOSARCOMA
In this juvenile (embryonal) rhabdomyosarcoma of the nasopharynx, note the neoplastic cells more recognizable as of muscle derivation. X63.

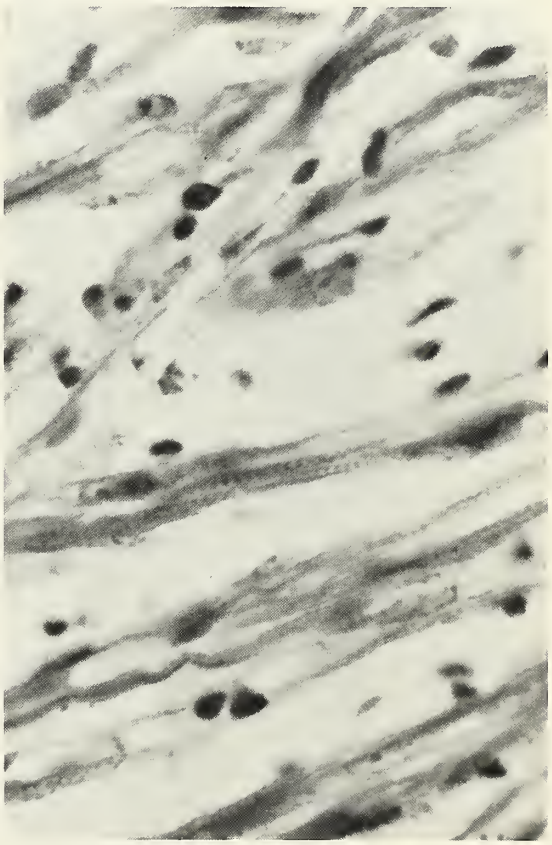

Figure 175
RHABDOMYOSARCOMA
In better differentiated juvenile (embryonal) rhabdomyosarcoma, cross striations are noted occasionally. X320.

cells. The round cells have scant to moderate amounts of cytoplasm and appear indifferent in their cytomorphology. They may resemble malignant lymphoid cells. The spindle cells are slim, long cells with bipolar processes. Nuclei are usually single and central, but may be eccentric. The cytoplasm is typically eosinophilic. The overall pattern may be loose and myxoid or compact. Longitudinal and cross striation may or may not be seen in this type.

Alveolar rhabdomyosarcoma. This form (figs. 176, 177) consists of one or more layers of neoplastic cells arranged more or less in a trabecular pattern intermixed with vascular connective tissue. The central parts of the trabeculae appear empty (hence alveolar) or contain varying numbers of free floating cells. Some of these cells may be large and multinucleated or round to oval or straplike. Both longitudinal and cross striations may be found in these cells.

Pleomorphic rhabdomyosarcoma. Likened to dedifferentiated adult skeletal muscle (fig. 178), the pleomorphic rhabdomyosarcoma is composed primarily of anaplastic pleomorphic spindle cells arranged in whorls, clusters, or even fascicles in a random pattern. The cells are often broad and elongated. Straplike or ribbon-shaped cells with multiple nuclei and eosinophilic cytoplasm are prominent. The cells exhibit longitudinal striations and myofibrils and, less often, cross striations.

Sarcoma botryoides. This is not an appropriate histologic subtype, even though its appearance does have some distinctive microscopic features. Deriving its name from a gross resemblance to a cluster of grapes, sarcoma botryoides is most often an embry-

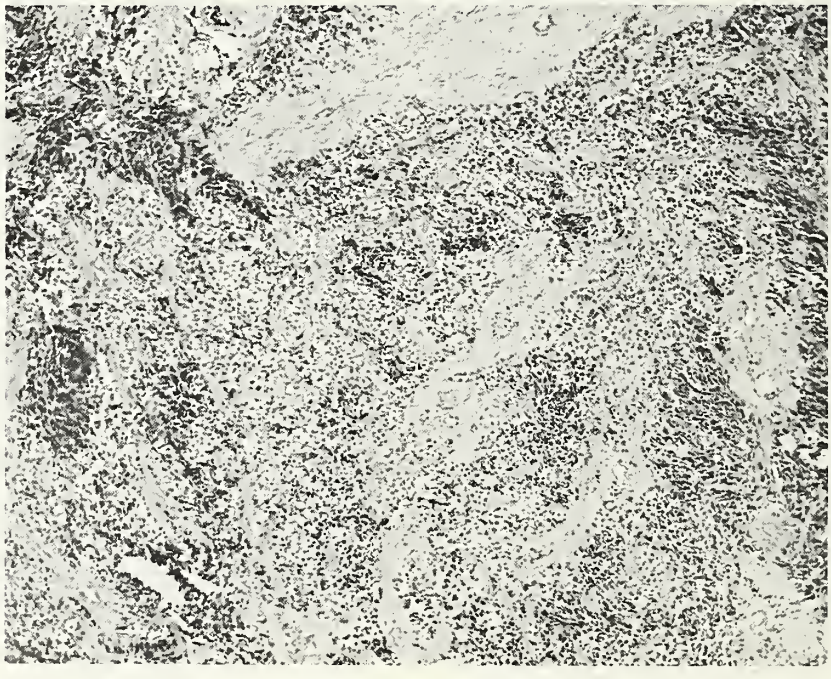

Figure 176
RHABDOMYOSARCOMA
A juvenile rhabdomyosarcoma of the alveolar type. X63.

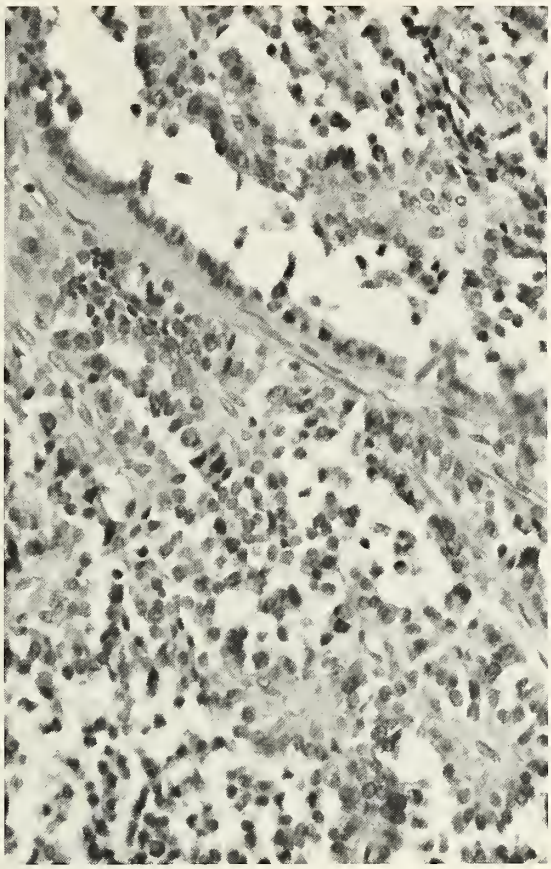

Figure 177
RHABDOMYOSARCOMA
The obvious alveolar micromorphology is noted in this juvenile rhabdomyosarcoma. X125.

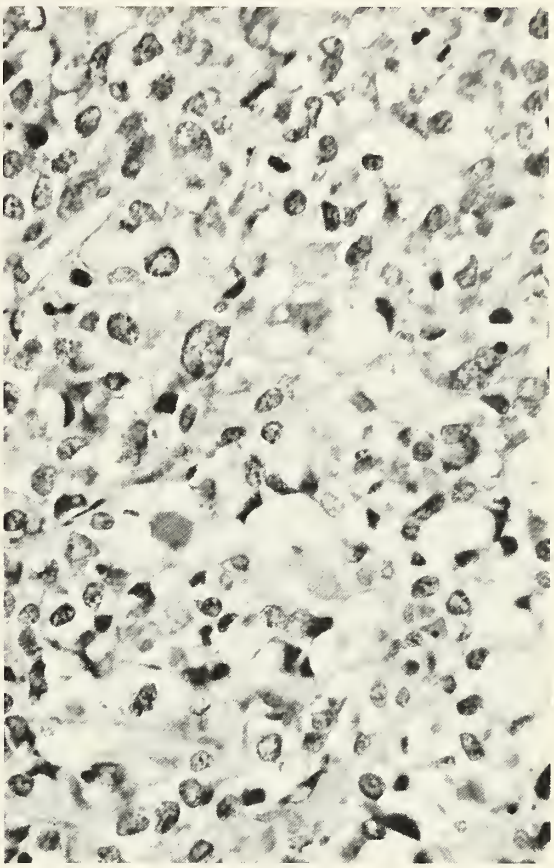

Figure 178
RHABDOMYOSARCOMA
This pleomorphic or adult type rhabdomyosarcoma suggests a malignant neoplasm of skeletal muscle. X400.

onal rhabdomyosarcoma in which anatomic site allows outgrowth into an open space, e.g., nasopharynx or sinus. These tumors have a more or less compact layer of small lymphocyte-like cells beneath the mucous membrane (so-called cambium layer), below which the tumor has a loose, more sparse structure and the cells a more haphazard arrangement.

Treatment and Natural History. Advances in treatment of rhabdomyosarcoma by combination treatment (surgical procedure, irradiation, and multiple drug chemotherapy) have altered the formerly dismal prognosis for these tumors. The head and neck as an anatomic region shares the enhanced prognosis with other regions of the body. Parameningeal sites, such as the nasopharynx, however, are still not conducive to long survival (Batsakis et al.).

Age, sex, histologic type, and the ability to metastasize are not determinants for response to treatment and survival. The principle factor is the extent of disease and, hence, clinical stage (Maurer).

As well as spreading to contiguous structures, rhabdomyosarcoma manifests a high incidence of distant metastases, either at the time of diagnosis or during the course of the disease. The incidence of 20 percent of distant spread at the time of diagnosis reported by Okamura and associates is quite representative of rhabdomyosarcomas as a group. Metastasis to lymph nodes appears to be modified by site of origin of the sarcoma (Lawrence et al.).

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CARTILAGINOUS TUMORS

The majority of neoplasms of cartilage origin in the head and neck behave in a malignant or, at least, locally aggressive manner (Batsakis et al.).

Many lesions containing cartilage are classified under "chondroma." Included in this category are lesions such as cartilaginous spurs of the nasal septum and osteochondromas. The latter are more appropriately regarded as exostoses. The exostosis exists in solitary or multiple forms and is usually clinically silent. The solitary osteochondroma (exostosis) is rarely premalignant, but the incidence of complicating chondrosarcoma in patients with multiple osteochondromas is significant (Unni and Dahlin). The relationship of the osteochondroma to pure benign cartilage tumors is remote. The latter (chondroma) also exist in multiple and solitary forms and may be central (endosteal) or peripheral.

The histopathologic distinction between a chondroma and a histologically low-grade chondrosarcoma is notoriously difficult. In that respect, it is to be appreciated that many of the fine structural features of low-grade chondrosarcoma cells are also found in cells of normal hyaline cartilage. Erlandson and Huvos have stated: "One would be hard pressed to point out differences between normal chondrocytes and neoplastic cartilage cells in low-grade chondrosarcomas." As may be expected, there are also few histochemical differences between benign cartilage and low-grade chondrosarcoma (Kindblom and Angervall).

The above should underscore the problems dealt with by the pathologist on encountering a tumor of cartilage in the head and neck. Lack of sufficient followup for many so-called chondromas further mars any attempt toward understanding of these lesions.

CHONDROMA

In the head and neck, chondromas have been most often reported from regions other than the maxilla and mandible, once again illustrating the suspect nature of cartilage tumors in those sites. Table 11, from the study of Kilby and Ambegaokar, presents the locations of 128 chondromas. In the AFIP-OTR material there were 10 patients with chondroma of the temporal bone distributed in the external ear, middle ear, and in the inner ear osseous labyrinth. The cartilaginous tumors of the larynx will be discussed in a later separate presentation. Sinonasal and pharyngeal chondroma is usually an asymptomatic lesion and is often found incidentally during examinations. They are polypoid, smooth-surfaced nodules that may vary from 0.5 cm to 2.0 cm in size. Three centimeters

Table 11

UPPER RESPIRATORY AREA CHONDROMAS SITE OF ORIGIN

Location	Percentage
Ethmoids and nasal cavity	50
Nasal septum	17
Maxilla and maxillary antrum	18
Hard palate	6
Nasopharynx, sphenoid sinus, eustachian tube	6
Alar cartilages	3

is usually the maximum size of a chondroma. The mucosa overlying the lobulated mass is not ulcerated. Their consistency is usually firm but, on occasion, may be soft and cystic. In general, nasal chondromas are not radiopaque.

Their origin from noncartilaginous areas is considered to rest on a focal hypertrophy of heterotopic islands in the nasopharyngeal mucosa and lamina propria.

Microscopically, the lesions consist of lobulated, well differentiated hyaline cartilage. There is only minimal nuclear atypia, if any (fig. 179).

The therapeutic approach is that of assured complete surgical removal and it is mandatory that an adequate margin of normal tissue is removed with all cartilaginous tumors.

Figure 179
CHONDROMA
The histology of a chondroma of the nasal septum is that of essentially normal cartilage. X160.

CHONDROSARCOMA

Frequency. Chondrosarcomas of the jaws and maxillofacial skeleton (sinonasal tract) are certainly not common neoplasms. Kragh and associates cited 10 patients from the Mayo Clinic files over a 50-year period. Memorial Hospital, New York City, recorded only 18 chondrosarcomas of the head and neck (exclusive of the larynx) from 1932 through 1968 (Arlen et al.). The Japanese literature contained only 35 patients reported in a 50-year period (Sato et al.). An estimate of the incidence of chondrosarcomas of the upper airway and temporal bone would be 1.25 percent of all chondrosarcomas in the body.

In the AFIP-OTR material, there were four chondrosarcoma patients with the neoplasm arising in the area of the jugular fossa and involving the temporal bone.

Incidence. From this relatively small experience, some demographics of the malignancy may be derived. Chondrosarcomas of the maxilla (sinonasal tract) occur more frequently than those of the mandible. Sex distribution is nearly equal, but there is a tendency for women to manifest more maxillary than mandibular chondrosarcomas. For chondrosarcomas of extra-facial sites, there is a peak incidence in the sixth decade. Chondrosarcomas of the upper airway have demonstrated the most common age of involvement as near 60 years, but with nearly half of the reported examples occurring during the third and fourth decades. In the maxilla, there is a preference for the anterior area, palate, or the vicinity of the lateral incisors and canine teeth. When origin is in the mandible, the premolar and molar regions, the symphysis, and the coronoid and condylar processes are sites of predilection.

Pathogenesis. The preference for chondrosarcomas to arise from specific areas of the upper airway has given rise to speculation over the tissue of origin (Myers and Thawley). Assumed but not proven, is origin from vestigial cartilaginous rests. Other sources of origin may be areas of chondroid bone found in the alveolar ridges and mandibular angles and mesenchymal cells with the potential to differentiate into chondroblasts.

Radiologically, chondrosarcomas are destructive lesions with single or multiple radiolucent areas. Mottled calcification may be present. Chondrosarcomas share with osteogenic sarcomas a uniform widening of the periodontal membrane space.

Clinical. The most common clinical signs of chondrosarcoma of the facial and jaw bones are swelling, expansion of the buccal and lingual plates, and premature eruption or exfoliation of teeth. Pain, trismus, neural sensory deficiency, and nasal signs relate to extension of the neoplasms. The duration of symptoms may be long before the patient seeks medical advice, but usually averages less than a year.

Gross. The chondrosarcoma is a firm, lobulated mass, often of a spectacular size, especially in the septo-ethmoidal area. The mucosa overlying the lesion is often intact, but may be ulcerated due to pressure necrosis.

Microscopic. Light microscopic features for diagnosis of chondrosarcoma include increased numbers of cartilage cells with plump nuclei, more than occasional binucleate cells, and presence of multinucleated giant cartilage cells (figs. 180-182). In the head and neck area, the prognostic significance appears directly related to the cytologic differentiation of the chondrosarcoma. A determination of whether the neoplasm is of low (well differentiated) or high (poorly differentiated) micromorphology appears to suffice in chondrosarcoma of the upper respiratory tract area.

In considering the histologic differential diagnosis in dealing with a chondrosarcoma, there may be difficulty in separating it from the occasional mixed tumor (pleomorphic adenoma) of the upper respiratory tract area that possesses a prominent pseudocartilaginous portion. The histologic presence of some epithelial cells within the mixed tumor is expected and this should be the diagnostic clue.

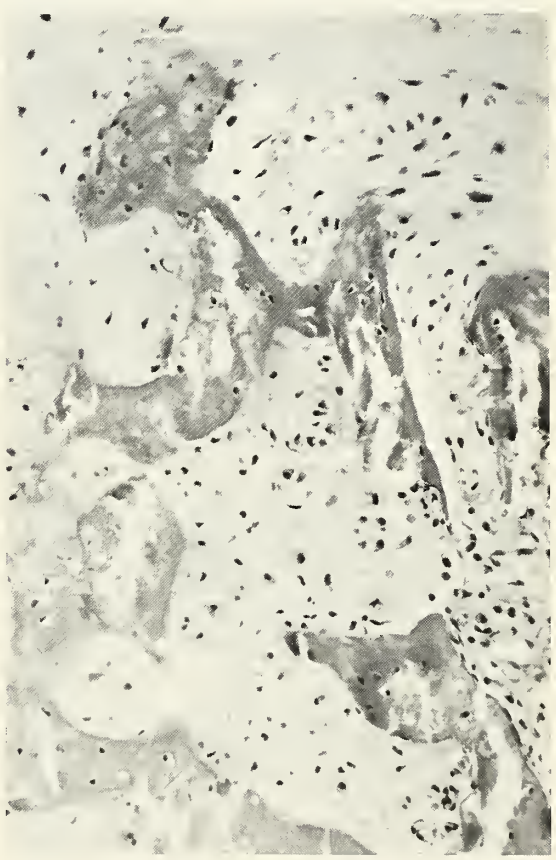

Figure 180
CHONDROSARCOMA
Increased cellularity and pleomorphism differentiates this neoplasm from a chondroma. The presence of osseous elements is a frequent feature of the lower-grade chondrosarcomas. X160.

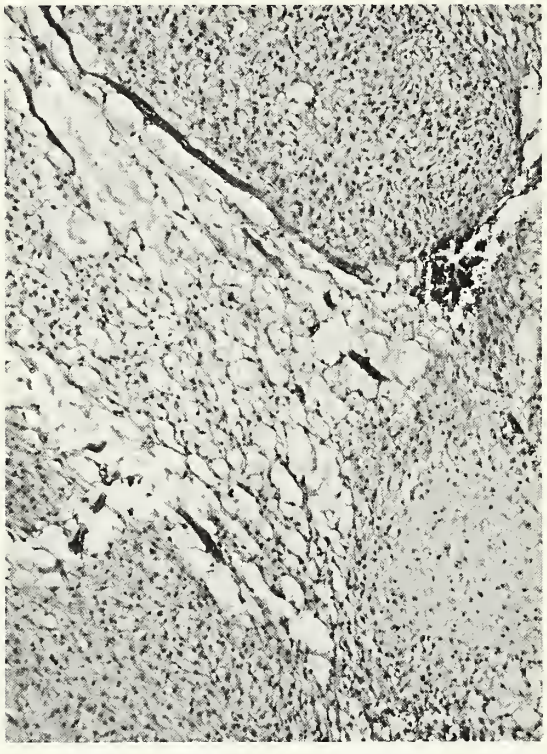

Figure 181
(Figures 181 and 182 are from the same patient)
CHONDROSARCOMA
A more undifferentiated histology of a chondrosarcoma of the sinonasal tract. X63.

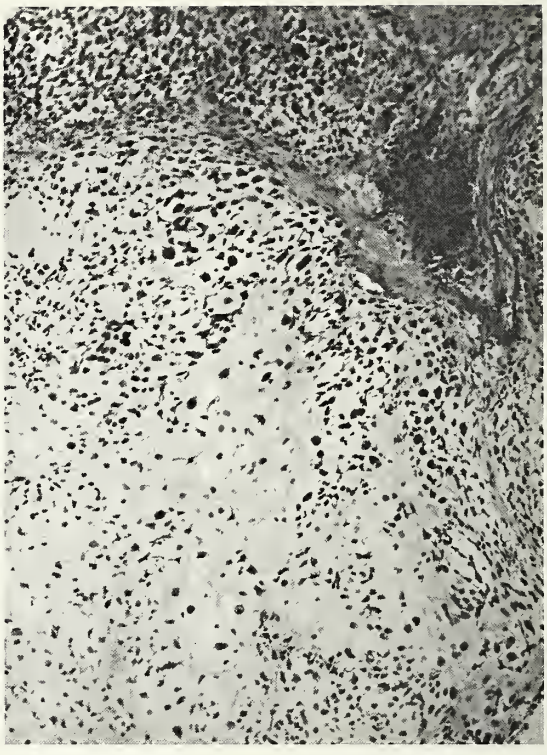

Figure 182
CHONDROSARCOMA
Note the increased cellularity, anaplasia, and mitotic activity in this chondrosarcoma. X160.

The prognosis of any chondrosarcoma is dependent upon three factors: (1) location of the primary; (2) adequacy of primary surgical removal; and (3) histologic grade of the neoplasm (Fu and Perzin). The first two are predominant.

Natural History. Patients with chondrosarcoma involving facial bones and sinonasal tract areas usually have a slow, yet progressive, course of their disease and may survive for prolonged periods with multiple recurrence. Death results from uncontrolled local disease with extension to the base of the skull and into the cranial cavity. Distant metastases, while a constant threat (especially in patients with multiple recurrences) are few. Fu and Perzin reported an 8 percent incidence of metastases in their review of published cases of chondrosarcoma of the sinonasal tract and nasopharynx.

Five-year survival statistics tell only a partial story, since death from tumor aggression may occur after that time. Fu and Perzin record a 62 percent five-year survival; Kragh and associates, a 40 percent five-year survival. These are to be compared to a 54 percent five-year rate for chondrosarcomas of extra facial sites.

Treatment. At the present time, radical resection is the only treatment that offers significant prospects for cure. Prognosis improves almost in direct relationship to the

width of the margin of normal tissue removed encompassing the neoplasm at surgical resection. Fu and Perzin indicate the only lesions to recur are those in which the neoplasm extended to the lines of excision.

MESENCHYMAL CHONDROSARCOMA

This neoplasm is a distinctive type of chondrosarcoma that exists in both skeletal and extraskeletal forms, has predilection for the facial bones and ribs, and rarely affects tubular bones. Over one third of the reported examples have been in soft tissues and, here also, the head and neck (principally the orbit) are typically the sites of involvement (Bloch et al.).

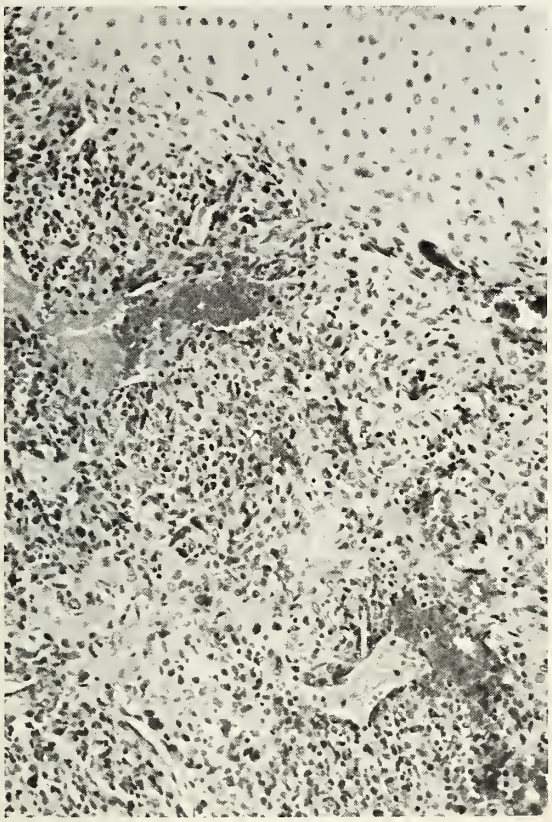

Figure 183
MESENCHYMAL CHONDROSARCOMA
The majority of the cells support an undifferentiated malignant tumor. The distinctive neoplastic cartilaginous foci, however, is diagnostic of mesenchymal chondrosarcoma. X160.

Pathologic diagnosis of this lesion is established by the finding of a richly cellular neoplasm composed of undifferentiated cartilage (fig. 183). The presence of this cartilage histology is essential to the diagnosis. Failure to find the cartilaginous "islands" often leads to a misdiagnosis of hemangiopericytoma.

The neoplastic entity requires radical surgical removal. Simple excision, radiation, or curettage leads to a nearly predictable recurrence and, worse, metastases and death. Metastases may make their appearance after long latent periods. A hematogenous spread, primarily to the lungs, is more common than lymphatic dissemination.

Extraosseous (nonmesenchymal) chondrosarcomas of the jaws and facial bone areas are almost unique. They take their origin from periosteal connective tissue elements that have differentiated along chondroblastic lines.

CARTILAGE TUMORS OF THE LARYNX

Cartilaginous tumors of the larynx are rare. Indicative of their rarity are statistics available from the Massachusetts Eye and Ear Infirmary (Huizenga and Balogh) and AFIP-OTR (Hyams and Rabuzzi). In the former institution 20 cases among 5000 primary laryngeal neoplasms (30 years) were reported. The AFIP-OTR series entails 31 cases added to the Registry between 1929 and 1969.

Sites of Tumor. Anatomic sites of involvement in the larynx (fig. 184) are presented in Table 12. This frequency distribution is in general agreement with previously published reports. The largest group develops from the cricoid cartilage, with a predilection for the

Figure 184
CHONDROSARCOMA
This larynx specimen from an elderly male demonstrates the typical anatomic location (posterior lamina of the cricoid cartilage) of a chondrosarcoma. (Courtesy of Dr. Paul S. Milley, Buffalo, NY.).

Table 12

CARTILAGINOUS TUMORS OF THE LARYNX*

Site	Histologic Classification	
	Chondroma	Chondrosarcoma
Cricoid cartilage	3	20
Thyroid cartilage	2	5
Arytenoid	0	4
Epiglottis	2	0
Vocal cord	9	0
Total	16	29

*Based on the series of Hyams and Rabuzzi; Huizenga and Balogh

anterior surface of the posterior lamina. The AFIP-OTR series also contains a relatively large number arising in the soft tissues of the vocal cord. To our knowledge, no reported cartilaginous neoplasms have arisen from the corniculate, cuneiform, or triticea cartilages.

Histogenetically, it is pertinent to note that nearly all documented cases of chondrosarcoma of the larynx have arisen from hyaline cartilage and show no evidence of elastic tissue differentiation. There were chondromas (two in the epiglottis and nine in the true vocal cord) that supported the histology of elastic type cartilage, according to the series of Hyams and Rabuzzi.

Incidence. The cartilaginous tumors of the larynx are predominantly of the fourth through sixth decade of life and manifest a distinct male predominance. This age is in contrast to the cartilaginous neoplasms (particularly chondrosarcomas) of extralaryngeal origin, which affect mainly young and middle-aged adults. It is, however, in consort with the age incidence of cartilaginous neoplasms of the facial bone.

Clinical. Clinical presentations are nonspecific and relate to a slow, yet progressive, encroachment of the subglottic space, i.e., hoarseness, poor voice, or dysphagia. Rarely, mass growth is extralaryngeal.

At laryngoscopic examination, the chondromas are usually 2 cm or less, while the chondrosarcomas are larger than the 2 cm diameter. The tumors appear as smooth, encapsulated masses located beneath the mucosa. Roentgenograms of the soft tissue of the larynx, planograms, and laryngograms are useful to delineate the lesion and its points of attachment. They demonstrate a smooth surfaced, homogeneously dense, unilateral tumor that bulges into the airway. A mottled calcification in the region is seen in approximately 80 percent of the lesions. Tomograms may permit identification of tumor penetration through the cricoid lamina to the external perichondrium. Biopsy of the tumors may be difficult or impossible because of the hardness of the mass.

Microscopic. The histologic qualification of chondroma given by Hyams and Rabuzzi is that the tumor duplicates the histology of normal cartilage. While the chondroma may exhibit an increased cellularity, the individual cells retain a uniform morphology.

The criteria for chondrosarcoma utilized are those of Lichtenstein and Jaffe and Spjut and associates: (1) pronounced irregularity in size of the cells and their nuclei; (2) presence of numerous cells and their nuclei; (3) pronounced hyperchromatism of the nuclei; and (4) any large or giant cartilage cells with single or multiple nuclei or with clumps of chromatin. The presence of bone in the neoplasm does not alter the classification or prognosis.

Treatment. Chondrosarcoma of the larynx, for the best prognosis, requires a wide local excision encompassing a margin of normal tissue (Hyams and Rabuzzi). In the AFIP-OTR material, all patients with laryngeal chondrosarcoma who were considered cured had undergone total laryngectomy. The chondromas of the larynx were usually small (mostly under 2 cm in diameter) and usually required local surgery only.

Spread. Chondrosarcomas of the larynx are primarily local invaders, but distant metastases have been reported. Local recurrence occurs in approximately one-fourth of the cases, but is not catastrophic and is locally treatable.

Cartilaginous metaplasia within the soft tissues of the larynx is not an uncommon finding. The lesions are almost always solitary, small, and are found in the vestibular folds or vocal cords. In some patients, these metaplastic foci may reach a size which initiates symptoms. Often the metaplasia is in relation to trauma, e.g., vocal nodule. These metaplastic cartilaginous foci must be differentiated histologically from the bilateral cartilage nodules that are seen normally in the anterior portion of the thyroarytenoid ligament (vocal ligament) and from the true chondromas of the true vocal cord that have been described by Hyams and Rabuzzi. These metaplastic nodules do not arise from

pre-existing cartilage and do show fibroblasts at the periphery of the lesions, with a transition of chondrocytic cells near the center (Hill et al.). Intercellular stromal acid mucopolysaccharide is prominent and aggregates of elastin fibers can be found throughout the lesions.

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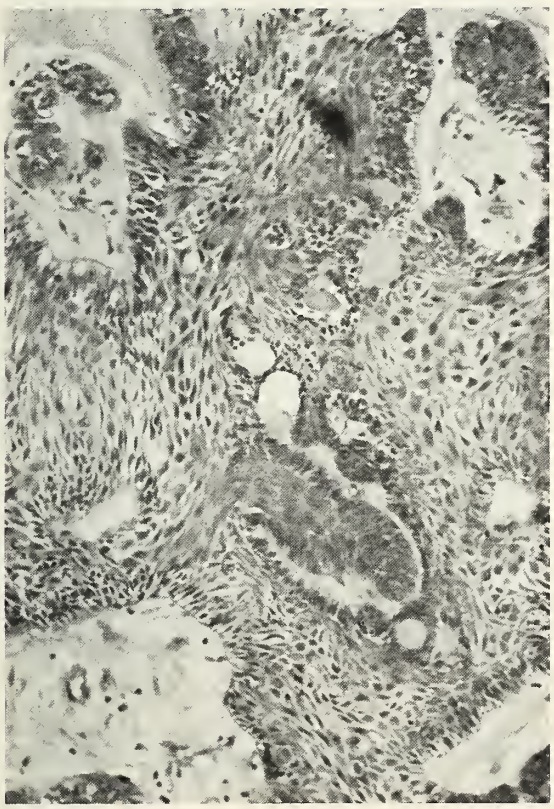
SUGGESTIVE ODONTOGENIC TUMORS

AMELOBLASTOMA

The ameloblastoma, which is usually a benign but locally invasive neoplasm arising from the odontogenic apparatus, does involve the sinonasal tract, particularly the maxillary sinus (figs. 185, 186). The temporal bone may even be the rare primary site of the neoplasm. The subject of ameloblastoma is well covered in texts dealing with dental neoplasms, including the Atlas of Tumor Pathology, Fascicle 24, Second Series, Intraosseous and Parosteal Tumors of the Jaws, and the reader is referred to such publications.



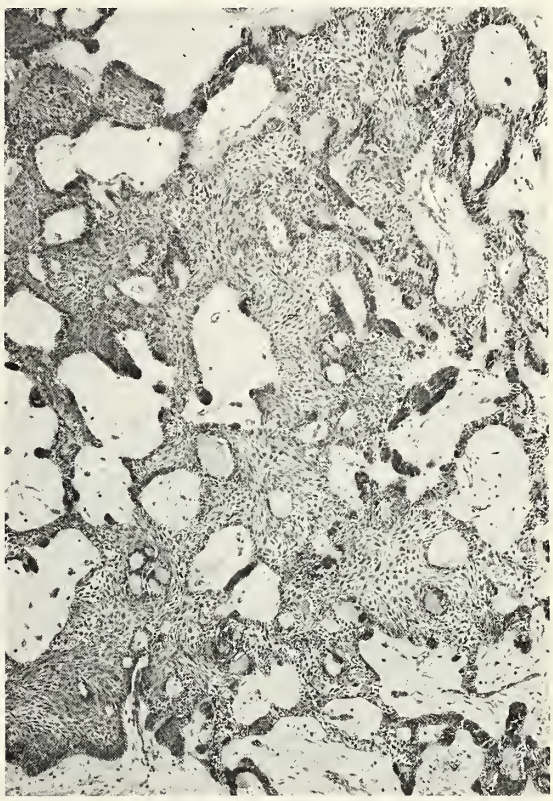


Figure 185
(Figures 185 and 186 are from the same patient)
AMELOBLASTOMA
A histologic section of an ameloblastoma of the maxillary sinus area with the neoplastic epithelium arranged in irregular masses and as a network. The tumor mass is bounded by a layer of columnar cells and includes cells resembling stellate reticulum. X63.

Figure 186
AMELOBLASTOMA
Higher magnification of the previous illustration emphasizes the histologic details. X160.

MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY

SYNONYMS AND RELATED TERMS: Melanotic progonoma; melanotic adamantinoma; retinal anlage tumor; melanoameloblastoma; pigmented epulis.

Melanotic neuroectodermal tumor of infancy is a rare, essentially benign neoplasm, felt most likely to be of neural crest origin (Zajtchuk et al.; Johnson et al.; Cutler et al.), originating most often in the anterior wall of the maxilla of an infant in the first year of life.

In the evaluation of 156 cases reviewed from the medical literature by Cutler and associates, 68.8 percent originated in the maxilla, 10.8 percent in the skull, 5.8 percent in the mandible, and 4.3 percent in the brain. The remaining 7.2 percent arose from sites outside the head and neck, such as genitourinary organs and bone. Diagnosis was first made under the age of one year in 95 percent of the patients. There was no sex or race predilection.

Clinical. The clinical presentation (Zajtchuk et al.) is typically described as a tumor arising from the anterior maxilla but not invading the overlying skin or mucosa. The blue-black appearance of the lesion is due to melanin

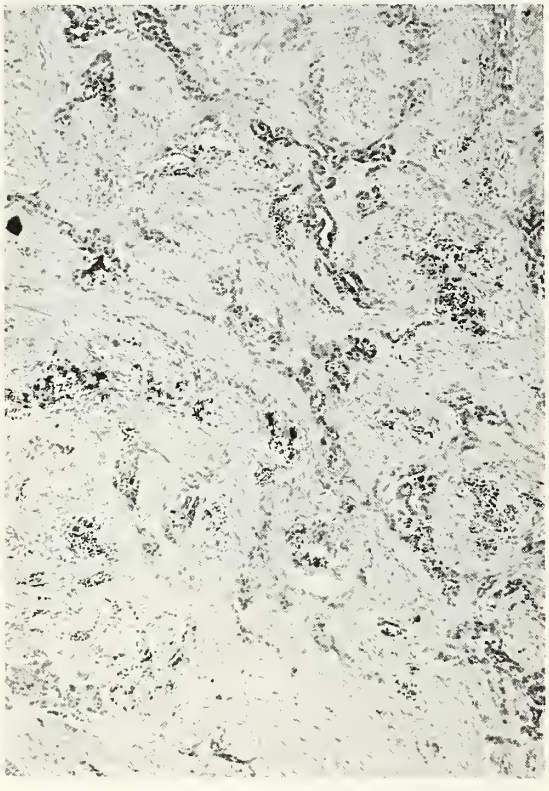


Figure 187
MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY
The melanotic neuroectodermal tumor of infancy consists of epithelial-like cells arranged in strands, an occasional gland or alveolar pattern, and accompanying small, darkly staining, lymphocytic-like cells, all in a cellular fibrous stroma. X63.

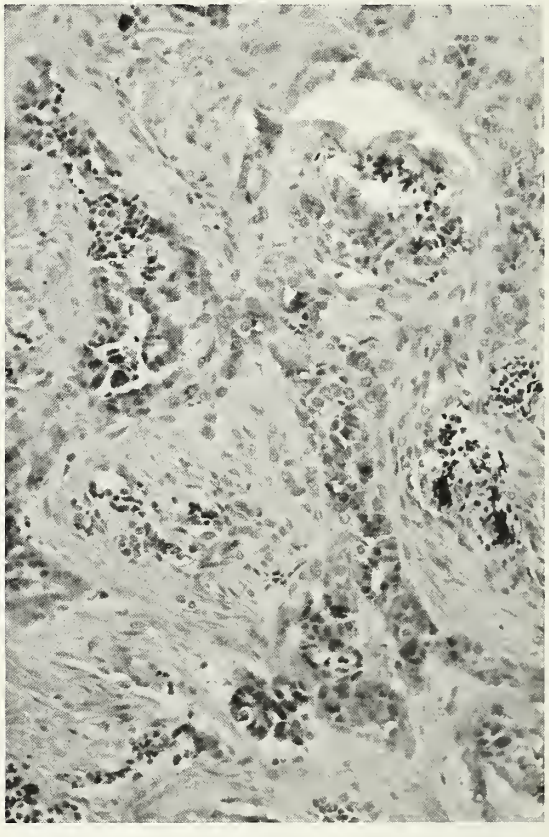


Figure 188
MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY
There is melanin in the epithelial-like cells and, to a lesser degree, in the lymphocytic-like cells. X160.

pigment deposits. The growth of the mass is so alarmingly rapid that biopsy and operation are usually done within two months from the time of its first notation. There is the rare report of malignant behavior in the melanotic neuroectodermal tumor of infancy (3.2 percent according to Cutler and associates). Laboratory findings are essentially normal, with a rare literature report of an elevated urinary vanillymandelic acid (VMA).

The lesion, grossly, has a blue-black, firm appearance and varies from 1 cm to 5 cm in diameter. Microscopically, the neoplasm consists of cords, strands, or an alveolar arrangement of epithelial-like cells usually containing readily identified melanin pigment granules (figs. 187, 188). Accompanying the tumor cells will be groups of small, dark cells resembling lymphocytes and occasionally containing melanin pigment. The stroma is a moderately cellular fibrous tissue. Ultrastructural studies revealed three different types of melanin granule formation (Cutler et al.), many cells having a single cilium and cell junctions of the "close" or "modified-tight" type, but no desmosomes.

Treatment is that of assured complete surgical removal without mutilation. There may be recurrence, particularly with inadequate removal, but malignant behavior is extremely rare.

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OSSEOUS TUMORS

Osseous tumors of the upper respiratory tract area and the temporal bone are an important part of the pathology of this anatomic area. Those interested in explicit coverage of the pathology of bone and cartilage tumors should consult Fascicle 5, Second Series, Tumors of Bone and Cartilage, by Spjut and associates. The following discussion will enumerate the various bone tumor entities of interest in the upper respiratory tract and temporal bone area and cite points of particular interest related to such entities. The benign fibro-osseous tumors (fibrous dysplasia and ossifying fibroma), the giant cell granulomatous tumors of bone, and chordoma will be discussed in more detail.

OSTEOMA

The osteoma (fig. 189) is defined by Spjut and colleagues as a protruding tumor mass composed of abnormally dense, but otherwise normal, bone formed in the periosteum. The sites of most common occurrence in the head and neck area are the frontal, ethmoid, and maxillary sinuses and the osseous external canal of the temporal bone. Osteomas and exostoses of the latter area will again be presented in the later section on temporal bone tumors.

Osteoma of the bones of the sinonasal tract is more common in males by nearly a 2 to 1 ratio. Multiple osteomas occur in the

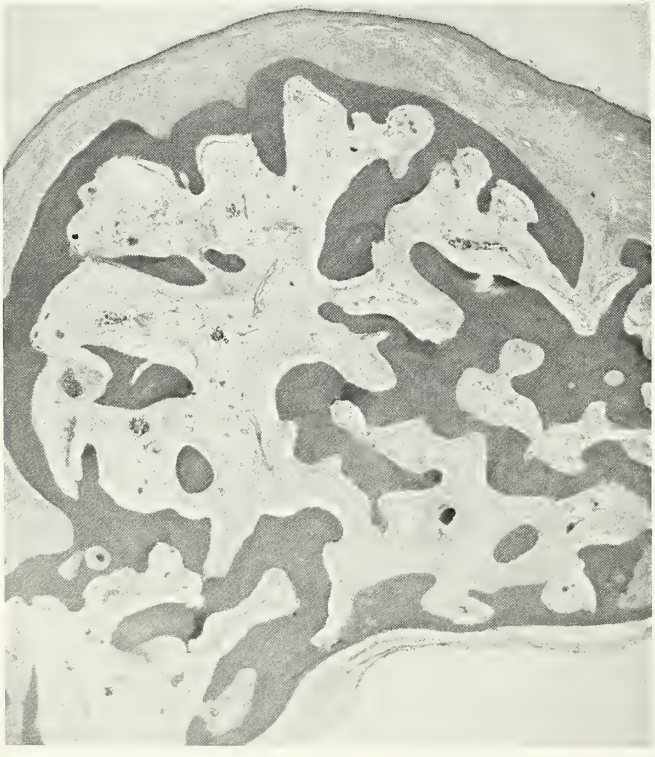

Figure 189
OSTEOMA
An osteoma of the external canal reveals the typical histology of the bony entity with a normal cortical and medullary architecture. X25.

skull and facial bones as a feature of the Fitzgerald-Gerald syndrome. These occur in association with polyps of the colon and rectum and nodules or cysts in or under the skin.

Small, asymptomatic osteomas without growth are best left alone. Others are treated by complete surgical removal with as minimal cosmetic deformity as possible (Atallah and Jay).

OSTEOID OSTEOMA AND OSTEOBLASTOMA

First of all, there is dispute as to whether these tumors are variations of the same process or separate neoplastic entities. Spjut and associates, in the Fascicle on Tumors of Bone and Cartilage, consider them as separate individual tumor entities and the reader is referred to their discussion. They define the osteoid osteoma (fig. 190) as a small, solitary, benign, painful lesion most commonly observed in the bones of the lower extremities and having distinctive symptoms, radiographic findings, and pathologic characteristics. The osteoblastoma is defined as an uncommon, solitary, benign, vascular, bone and osteoid-producing tumor that is rich in osteoblasts and most often involves vertebrae and long bones of the extremities. Neither of these neoplasms is common in the skull or facial bones.

There were 12 cases of osteoid osteomas reported in the jaws prior to 1976 (Farman et al.). Sex distribution was equal and ages ranged from 4 to 77 years, and most of the patients were young adults. If the diagnosis of osteoid osteoma is accepted as occurring in the skull bones, the treatment is local but complete block resection of the tumor.

The osteoblastoma (figs. 191, 192) is also a rare skull and facial bone tumor, and until 1976 only 13 cases of involvement in this area were reported in the world literature (Farman et al.). The AFIP-OTR material contains three patients with the diagnosis of osteoblastoma of the sinonasal tract area and two patients with temporal bone primary tumors. There was a slight male predominance in the reported literature cases, with the age range between 5 and 22 years.

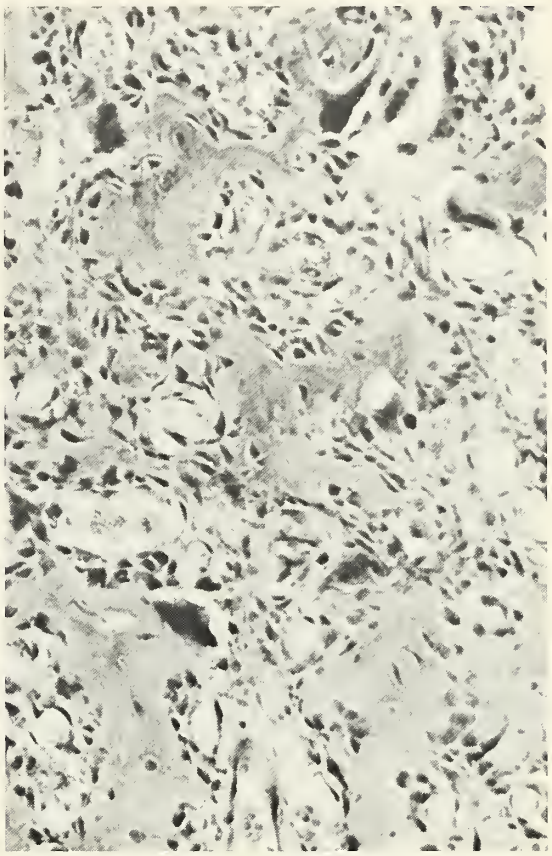

Figure 190
OSTEOID OSTEOMA
The nidus of an osteoid osteoma has a cellular, highly vascularized tissue made up of immature bone and osteoid tissue. X200.

In these neoplastic entities, it is imperative that a good clinical history and recent radiographic study information be available, together with the histologic material, to obtain the most reliable diagnosis. The

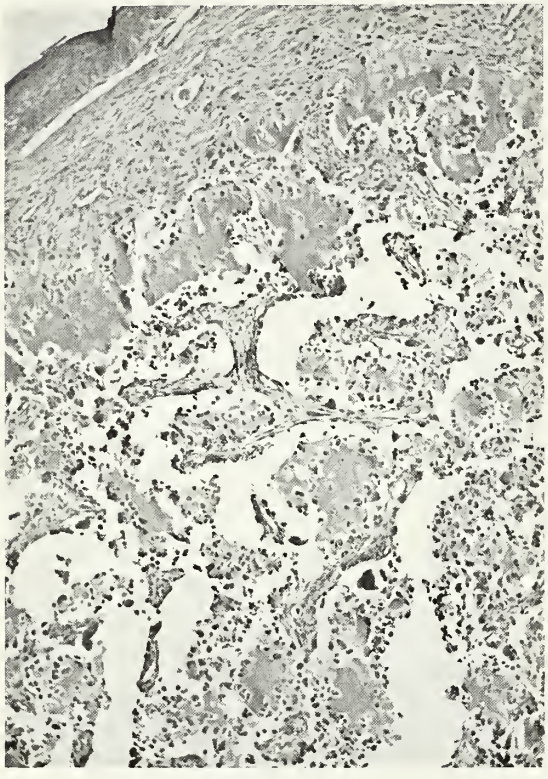

Figure 191
(Figures 191 and 192 are from the same patient)
OSTEOBLASTOMA
An osteoblastoma of the temporal bone is well demarcated from the surrounding tissue. X63.

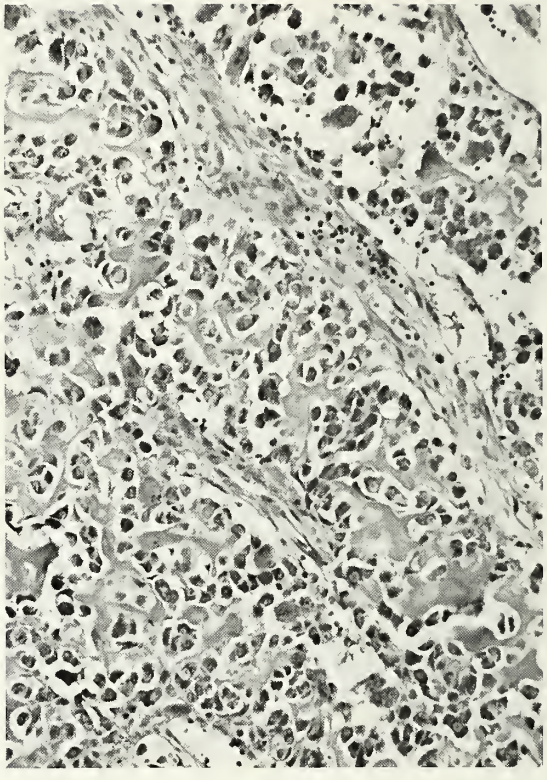

Figure 192
OSTEOBLASTOMA
Higher magnification of figure 191 supports the histology of a cellular, highly vascularized tissue made up of immature bone and osteoid tissue, with an unusual proliferation of osteoblasts. X160.

micromorphology alone can be misleading. The diagnostic differential includes osteosarcoma, juvenile ossifying fibroma, and ossifying cementifying fibroma.

The treatment is a nonradical en block surgical excision.

BENIGN FIBRO-OSSEOUS TUMORS OF THE BONES OF THE SKULL

Benign fibro-osseous tumors of bone that are of importance in the upper respiratory tract and temporal bone area are fibrous dysplasia and ossifying fibroma. There is controversy in the medical literature as to whether these two tumor entities should not be combined as one. Since these tumors do involve the head and neck area in an appreciable percentage, they will be discussed in some detail.

FIBROUS DYSPLASIA

Definition. Fibrous dysplasia of bone is a disease in which one or more bones may be affected by the replacement of their normal architecture with fibrous and osteoid tissue (Eversole et al.).

Etiology. The etiology of fibrous dysplasia is not definitely proven. In some minds, it is a hamartomatous condition resulting from failure of proper bone formation at the

embryonic or "woven" bone stage. Others have postulated a traumatic or vascular basis (Ramsey et al.).

Varieties. There are three forms of fibrous dysplasia: (1) monostotic; (2) polyostotic; and (3) the McCune-Albright syndrome. The latter is unusual (estimated to occur in 1 of 30-40 cases of fibrous dysplasia). This syndrome combines a polyostotic fibrous dysplasia with hyperpigmentation of skin and endocrine disturbances (precocious puberty and/or hyperthyroidism).

Site of Tumor. The skull is involved by fibrous dysplasia in approximately 15 percent of reported cases from the overall skeleton. The presentation is usually monostotic. The maxilla is most often the involved bone, followed by the mandible, lesser and greater sphenoid wings, the vertical and horizontal processes of the frontal bone, and temporal bone. The frontal and sphenoid sinuses frequently are obliterated by the tumor process. The bones of the other paranasal sinuses are rarely primarily involved. In the maxilla, there is no apparent site of predilection, in contrast to the mandible, where the angle is most commonly involved.

Incidence. The age of onset of maxillofacial bone fibrous dysplasia ranges from birth to over 50 years. Caucasians are much more often victims than blacks. There is a purported female dominance, but this disappears when polyostotic and disseminated forms are included in the evaluation (Ramsey et al.).

Clinical and Radiologic. The presenting complaint in over three-fourths of patients is swelling of the involved bone. Pain, as an accompaniment of maxillo-facial involvement, is infrequent and never as prominent as that observed in extracranial fibrous dysplasia. Deformity or functional disturbances may be present (fig. 193).

There is considerable variation in the roentgenographic findings and this relates to the character of the fibro-osseous tissue in the bone lesions (Obisesan et al.). Should the lesion be largely fibrous or contain cysts, then a radiolucent shadow is noted. If considerable ossification has taken place, a ground glass appearance will be seen. Many variations between these extremes can be noted. A lack of a sclerotic bone formation surrounding the lesion leads to poor demarcation. There is usually no periosteal reaction in the absence of fracture and, in most cases, the bony cortex is intact, although it may be eroded and thinned. Lesions in young patients, and in those present for a short time, tend to be radiolucent. Radiopacity increases with the age of the lesion.

Clinical laboratory findings manifest no significant changes in serum calcium or phosphorus concentrations, although serum alkaline phosphatase activity may sometimes be observed.

Gross. The gross appearance of fibrous dysplasia is also variable and depends upon the degree of ossification, vascularity, and associated hemorrhage. The color ranges from white to gray to pale yellow. The cortex is often a thin, expanded shell and the central defect is filled with fibrous tissue which may be soft and edematous, to tough, firm, rubbery, or gritty. Lesional margins are usually diffuse and indefinite. Ulceration of mucosa overlying the bony enlargement is uncommon unless the mass is traumatized. There is no capsule. Unlike the ossifying fibroma, a readily identified demarcation from uninvolved bone is usually not present (Eversole et al.).

Microscopic. The diagnosis of fibrous dysplasia, in typical cases, can be made by microscopic examination. In some, however,

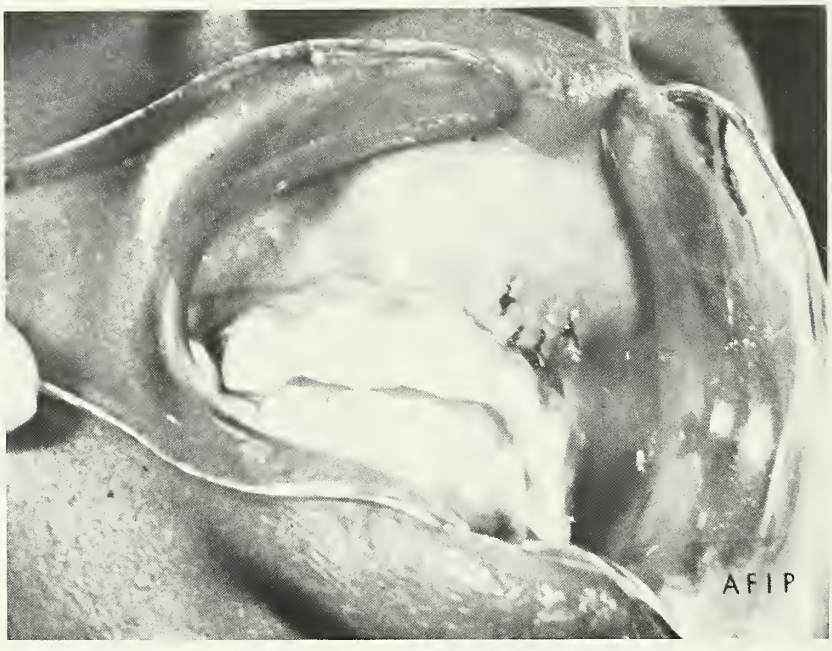

Figure 193
FIBROUS DYSPLASIA
This bone lesion is from the floor of the maxillary antrum of a six year old boy.

the diagnosis requires a combination of clinical, radiographic, and histologic findings.

The formation of bone, one of the major components of fibrous dysplasia, represents a metaplasia of the connective tissue component. The bony trabeculae are misshapen, irregular in size and distribution, and poorly oriented. They can take many forms, such as C-shapes, circles, and semilunar (Chinese) figures. There is an absence of osteoblastic rimming of the bony trabeculae. The interosteoid stroma may be variably cellular and vascular. Foci of macrophages and multinucleated giant cells may be found in areas of secondary degeneration of the stroma (figs. 194, 195).

The bone, under polarized light, appears woven rather than lamellar. There may be foci of lamellar transformation, and this should not detract from the diagnosis. Cartilage is rarely present and, if found, is almost exclusively in young patients.

The principal differential diagnosis is ossifying fibroma, although misinterpretation may lead to erroneous designations of osteogenic sarcoma, fibrosarcoma, ar a giant-cell lesion.

Treatment and Prognosis. Conservative surgical treatment is indicated for fibrous dysplasia disease of the facial skeleton when the extent of the lesion is such that disfigurement occurs. Except for solitary lesions of relatively small size, treatment should be aimed at resection rather than elimination of the tumor. Because the disorder may be progressive, surgical resection may have to be repeated. Radiation therapy is not recommended because of its questionable therapeutic value and the possibility of radiation-induced sarcoma (DeLathouwer and Brocheriou).

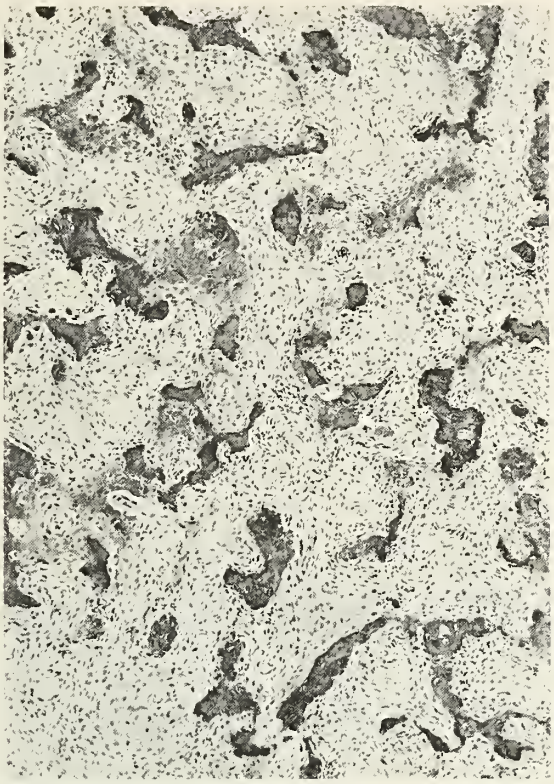

Figure 194
(Figures 194 and 195 are from the same patient)
FIBROUS DYSPLASIA
A fibrous dysplasia of the maxillary sinus area with the fibro-osseous tissue illustrating the so-called Chinese characters of the bony spicules. X63.

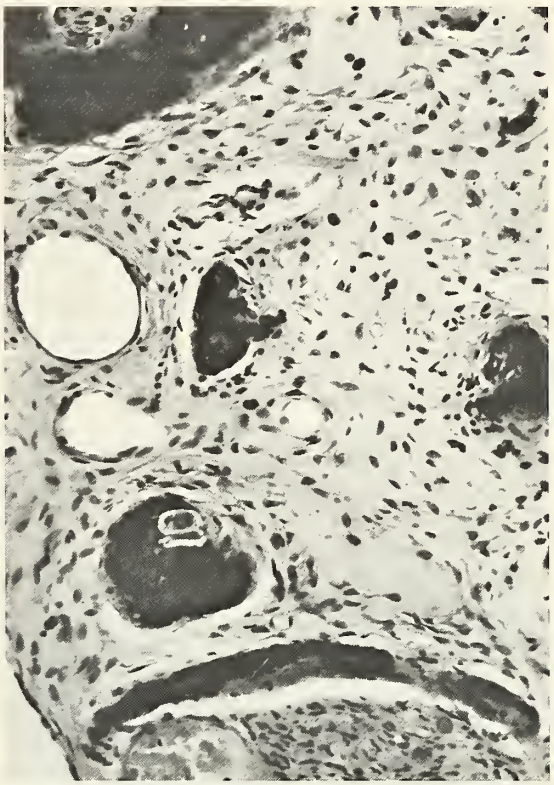

Figure 195
FIBROUS DYSPLASIA
Higher magnification of the previous illustration reveals the woven bone appearance with the lack of osteoblastic rimming. The fibrous stroma is unremarkable. X160.

The disease may become stable at puberty or, in aggressive lesions, death can be a sequela when there is direct extension into vital structures. According to Schwartz and Alpert, up to 1964 there were 28 patients reported with sarcoma arising in fibrous dysplasia. Many of these occurred following radiation, although some arose de novo.

OSSIFYING FIBROMA

Definition. Ossifying fibroma is an encapsulated neoplasm that consists of fibrous tissue containing varying amounts of metaplastic bone and mineralized masses that have rounded out linea and few entrapped cells.

Incidence. In the craniofacial bones, ossifying fibroma is a lesion which presents in two time periods: juveniles and after the second decade of life, most often in the third or fourth decades. In both age groups, there is a predilection for females (Hamner et al.; Langdon et al.).

Sites of Tumor. The majority of lesions are in the mandible, where the molar area, close to the roots of teeth, or periapical regions of the jaws are preferred sites. In the maxilla, the antrum is most often involved. In the AFIP-OTR data, there is the rare case limited to temporal bone.

Radiologic. The radiographic appearance of these lesions varies with the stage of maturity of the lesion. The ossifying fibroma at first appears as a relatively well demarcated radiolucency, but later becomes mineralized and relatively less well localized. Important, however, is the observation that regardless of the stage of maturation, ossifying fibromas are well defined and smoothly contoured lesions. This is in contrast to the diffuse borders manifested by fibrous dysplasia.

Gross. The tumors can vary from 1 to 2 cm to lesions of considerable size, 10 cm or more. They are gray-white to tan and firm. The surface has a gritty character owing to the bony spicules amidst a fibrous stroma.

Microscopic. The ossifying fibroma presents microscopically as evenly spaced spicules of bone rimmed with osteoblasts and osteoclasts within a fibrous stroma (figs. 196, 197). The spicules are randomly distributed within the fibrous stroma. Most of the spicules are centrally composed of woven bone, but there is evidence of a lamellar transformation at the periphery. Complete maturation to lamellar bone is observed only in isolated spicules. The fibrous stroma shows both loose and dense areas with occasional whorling. A prominent feature is an increased denseness of stroma with rounding of the fibroblasts near the bone spicules. Stromal hemorrhage, inflammation, and giant cells

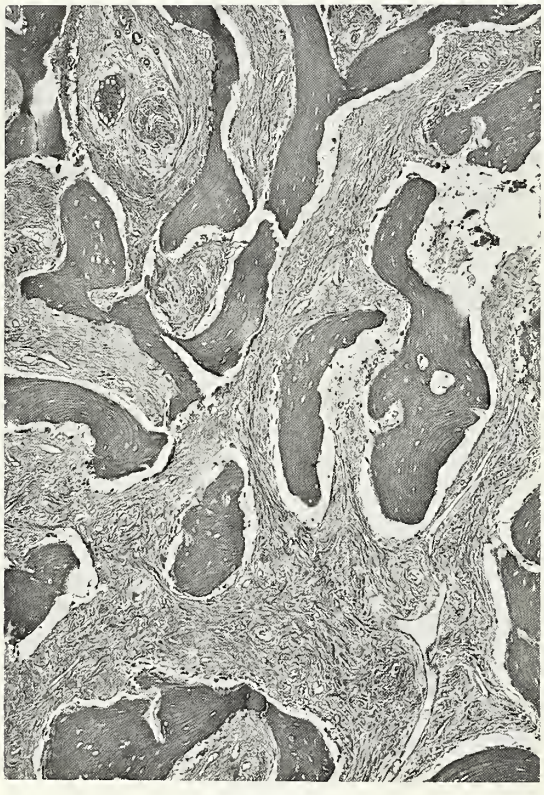

Figure 196
OSSIFYING FIBROMA
An ossifying fibroma of the maxillary sinus region depicts a fibro-osseous process with benign histology. X63.

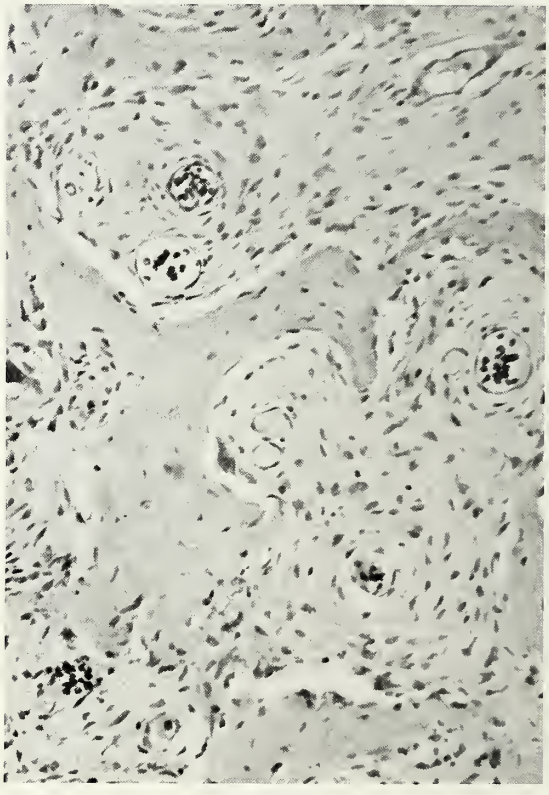

Figure 197
OSSIFYING FIBROMA
This ossifying fibroma is composed of mature woven bone with prominent osteoblasts rimming the spicules. The fibrous stroma shows loose and dense areas with whorling. X160.

are not seen in the unadulterated lesion. Radiologic circumscription is histologically translated into an often clearly evident capsule.

There is a variation of ossifying fibroma, involving mainly the juvenile, in which the flecks of bone are indistinguishable from the cementum of the odontogenic cementifying fibroma. This particular presentation has been labelled an active juvenile ossifying fibroma or psammomatous ossifying fibroma in the AFIP-OTR vernacular. The histology alone makes it impossible to separate the juvenile ossifying fibroma from the cementifying fibroma (figs. 198, 199). In juvenile ossifying fibroma there is a greater tendency for cementum-like trabeculae to be more numerous, ovoid, and heavily calcified than in the cementifying fibroma. In many respects, this cemento-osteoid lesion (juvenile ossifying fibroma) can be considered as one clinicopathologic entity (Hamner et al.; Langdon et al.).

Treatment. The usually well circumscribed nature of the ossifying fibroma and the juvenile variety lends itself to relative ease of surgical excision and, hence, to favorable therapeutic results. On occasion, however, in juveniles and in some maxillary lesions, the tumors assume an aggressive behavior and considerable local destruction of bone and recurrences ensue (Dehner).

Contrast with Fibrous Dysplasia. Fibrous dysplasia's histologic appearance differs from

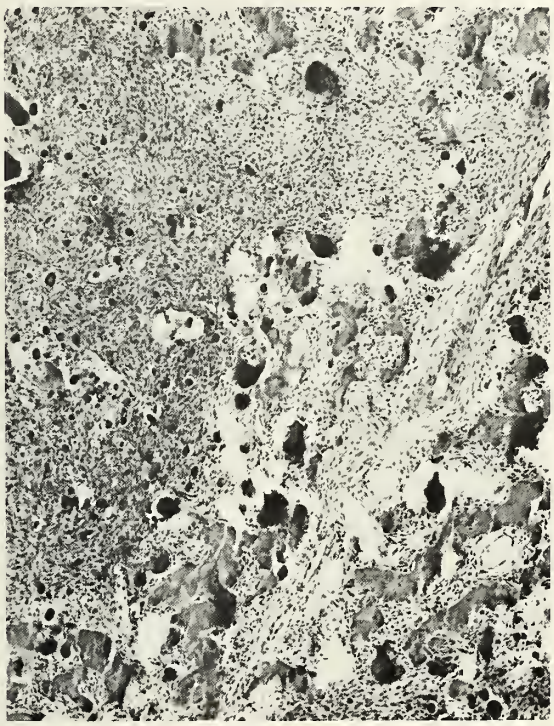

Figure 198
(Figures 198 and 199 are from the same patient)
OSSIFYING FIBROMA
This microscopic section of a so-called active juvenile ossifying (cementifying) fibroma of the ethmoid sinus region of a 17 year old female contains calcified cementifying bone and cellular fibrous tissue. X63.

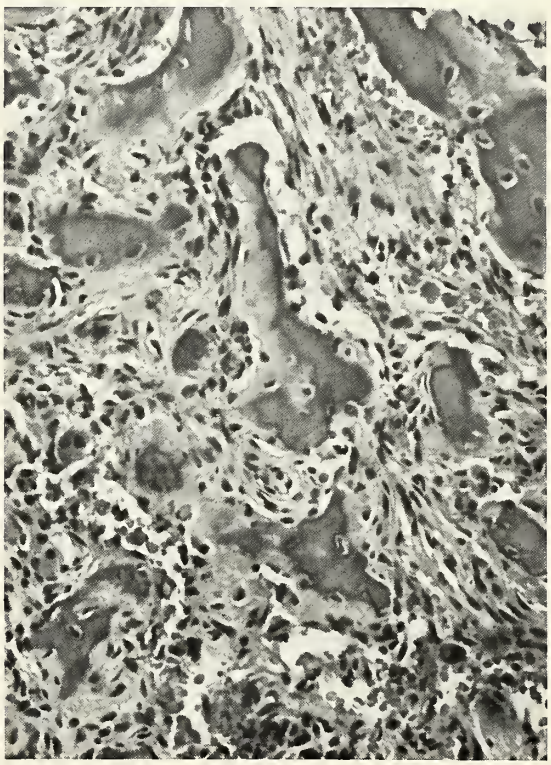

Figure 199
OSSIFYING FIBROMA
Higher magnification of the previous illustration emphasizes the cement-like bone spicules and cellular fibrous stroma. X160.

that of the ossifying fibroma (Kempson). In the former, there is immature woven or fiber bone which does not mature into lamellar types of bone. Woven bone has irregular bony trabeculae with feathery, irregular margins and osteolytic lacunae. Because fibrous dysplasia blends into surrounding bone, the margins are blurred and there is no apparent encapsulation. Table 13 presents contrasting features of ossifying fibroma and fibrous dysplasia.

GIANT CELL TUMORS

Most of the giant cell lesions of the skull and facial bones are considered to be non-neoplastic. The true giant cell neoplasm, analogous to the giant cell tumors of the long tubular bones, remains a controversial lesion as to occurrence in the facial skeleton. For information on the true giant cell, the reader is referred to the Fascicle on Bone and Cartilage Tumors by Spjut and associates.

GIANT CELL REPARATIVE GRANULOMA

The majority of giant cell lesions of the skull and facial bones are embraced by the diagnostic term "giant cell reparative granuloma." Peripheral and central forms exist. The term lacks accuracy, since the lesions are not granulomatous and are not likely reparative of any injury.

Clinical. Pain and swelling of several weeks' duration are the first symptoms. Pronounced expansion of the lesion during pregnancy may occur. Frontal headaches and diplopia are found in sphenoid presentations. Depending on the location within the temporal bone, the symptoms are conductive or sensorineural hearing loss, vertigo, and tinnitus.

Incidence. About half the patients with giant cell granulomas of the craniofacial bones are under 20 years of age when the diagnosis is made. An additional one fourth present with their lesions before reaching 30

Table 13

OSSIFYING FIBROMA VERSUS FIBROUS DYSPLASIA: CLINICOPATHOLOGIC FEATURES

	OSSIFYING FIBROMA	FIBROUS DYSPLASIA
Predominant Location	Mandible	Maxilla
Age/Sex	3rd-4th decades / females	1st-2nd decades / no sex preference
Major Radiographic Features	Circumscribed, well-defined borders	Merging, ill-defined borders
Major Histologic Features	Lamellar bones maturation with regular borders	Only woven bone with irregular borders
	Encapsulated	Unencapsulated
	Osteoblastic and osteoclastic activity	No osteoblastic or osteoclastic activity
	Parallel birefringent lines with polarized light	Randomly birefringent lines

years. Females are affected more than males.

Sites of Tumor. Most authorities agree that the giant cell lesions are most often found in the anterior portion of the maxilla and mandible, with a predilection for the former. The skull bones, the sphenoid and temporal bones are most frequently involved. In the temporal bone, the lesions have presented in the mastoid, petrous pyramid, jugular bulb, and middle ear (Hirschl and Katz; Glasscock and Hunt). There is a peripheral giant cell tumor that occurs in the submucosal area of the soft tissue gum area and, rarely, in the nasal cavity that presents an identical histology as that of the bone lesion.

Radiologic. Specific diagnosis of this radiolucent lesion cannot be made from radiographs alone, but the lesion is usually well demarcated, occasionally trabeculated, and, perhaps, multiloculated. There is usually an expansion and thinning of the cortex, and erosion of the cortex may also be seen (Shklar and Meyer).

Curetted fragments usually present as multiple hemorrhagic fragments of soft tissue.

Microscopic. Under the light microscope, the reparative lesion is composed of a fibroblastic network with focal areas of collagenization. Within this framework are multiple foci of hemorrhage surrounded by oval fibroblasts and many reactive-type multinucleated giant cells and a few chronic inflammatory cells (figs. 200, 201). The

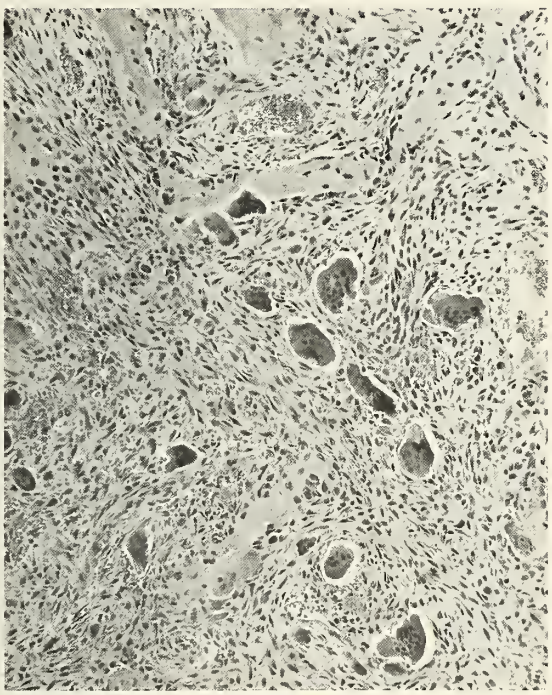

Figure 200
(Figures 200 and 201 are from the same patient)
GIANT CELL REPARATIVE GRANULOMA
This microscopic section of a giant cell reparative granuloma of the sinonasal tract area consists of a cellular fibroblastic network with focal areas of hemorrhage and scattered multinucleated giant cells. X63.

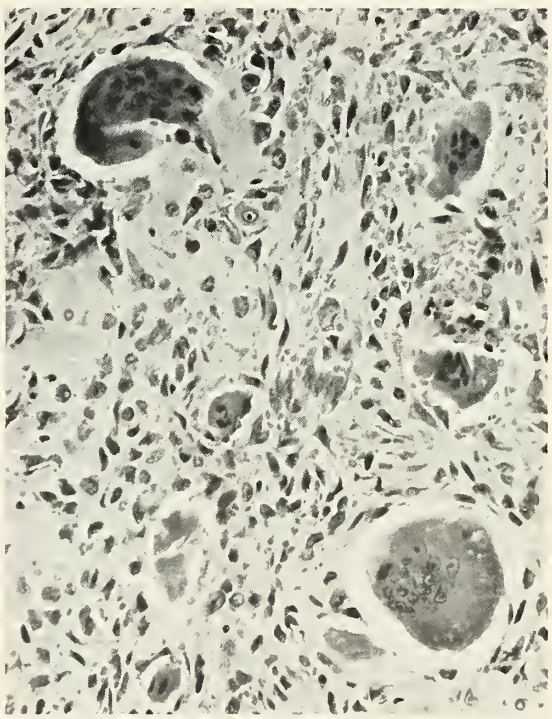

Figure 201
GIANT CELL REPARATIVE GRANULOMA
Higher magnification of figure 200 reveals the spindle-shaped fibroblasts with multinucleated giant cells and areas of osteoid. X160.

stroma is composed largely of spindle-shaped fibroblasts with a few giant cells and abundant hemosiderin, particularly in older lesions. Occasional spicules of new bone or osteoid may be present throughout. In patients over 20 years of age, the stroma of the lesion may be myxomatous.

The ultrastructure of peripheral giant cell granulomas has been reported by Adkins and associates and Bartel and Piatowska.

Differential Diagnosis. Several tumor entities composed at least in part of giant cells must be considered, including true giant cell tumor, cherubism, "brown-tumor" of hyperparathyroidism, aneurysmal bone cyst, giant cell reaction to known injury, some forms of histiocytoma and osteogenic sarcoma, as well as fibrous dysplasia. Table 14 presents a comparison of the clinical and histologic features of the giant cell reparative granuloma of bone and the true giant cell tumor of bone. The "brown-tumor" of hyperparathyroidism and cherubism cannot be differentiated on a histologic basis. In the latter, when the

Table 14

GIANT CELL REPARATIVE GRANULOMA VERSUS GIANT CELL TUMOR OF BONE*

	GIANT CELL REPARATIVE GRANULOMA OF BONE	GIANT CELL TUMOR OF BONE
Age of Patient	Usually under 21 years	Usually under 21 years
Clinical Behavior	Self-limited; may regress; seldom recurs; never metastasizes	Aggressive; no regression; recurs often; occasionally metastasizes
Histologic Features	Giant cells are grouped around hemorrhagic foci	Giant cells are uniformly dispersed and dominate the entire field
	Stroma shows oval cells and equally large number of spindled fibroblasts with zones of fibrosis and relatively few giant cells	Stroma is richly vascularized and is composed of plump, round, and oval cells
	Evidence of old and recent hemorrhage with hemosiderin	Recent hemorrhage is slight to moderate; hemosiderin is rare
	Giant cells are generally smaller, frequently irregular and elongated and have relatively few nuclei	Giant cells are generally larger, more rounded, and have a great number of nuclei
	Foci of osteoid and new bone function in the center of lesions are frequently present	Osteoid or new bone are not characteristically produced
Response to Therapy	Usually cured by curettage	Recurs if incomplete excision

*After Hirsch and Katz

morphologic pattern is combined with the clinical setting, the diagnosis of cherubism can be made. Clinically, patients are usually first seen between the ages of 2 and 5 years because of painless symmetrical swelling of the posterior mandible, rami, and maxillae. Radiographically, the lesions appear as well defined multilocular radiolucencies, sometimes containing displaced teeth. The pathogenesis is unknown, although a familial involvement is usually present.

The bone lesion of hyperparathyroidism (primary or secondary) is localized to an area of exaggerated bone resorption. In primary hyperparathyroidism, the so-called brown tumors frequently occur in the mandible and maxilla, where they are histologically indistinguishable from the reparative granuloma (Shklar and Meyer). Similar lesions in secondary hyperparathyroidism are much less frequent and, to date, have involved only the maxilla (Friedman et al.). Increased serum calcium, alkaline phosphatase, and parathyroid hormone levels will be required for diagnosis.

Natural History and Treatment. The giant cell reparative granuloma has a benign clinical course. Healing of the cystic lesion within bone occurs by means of new bone formation and sclerosis. Thorough surgical curettage usually affects a cure. Ten to 15 percent of lesions recur after incomplete removal. A smaller number behave in a more locally aggressive manner, and these cases have led to recommendation of excision rather than curettage (Andersen et al.).

GIANT CELL TUMOR OF THE LARYNX

There are eight cases of giant cell tumors arising in the larynx in the AFIP-OTR material. Whether these are from the ossified cartilage of the organ or the laryngeal soft tissue is difficult to establish. The ages run from the second to the seventh decade and the sex ratio is equal. The histology (figs. 202, 203) of two cases sent to the AFIP-OTR through the courtesy of Dr. Avram A. Jacobson, M.D., San Antonio, TX, is that of a prominent vascular pattern and suggests an aneurysmal bone cyst. These laryngeal giant cell tumors did not metastasize in any case; however, their size occasionally led to a laryngectomy because of airway obstruction. The

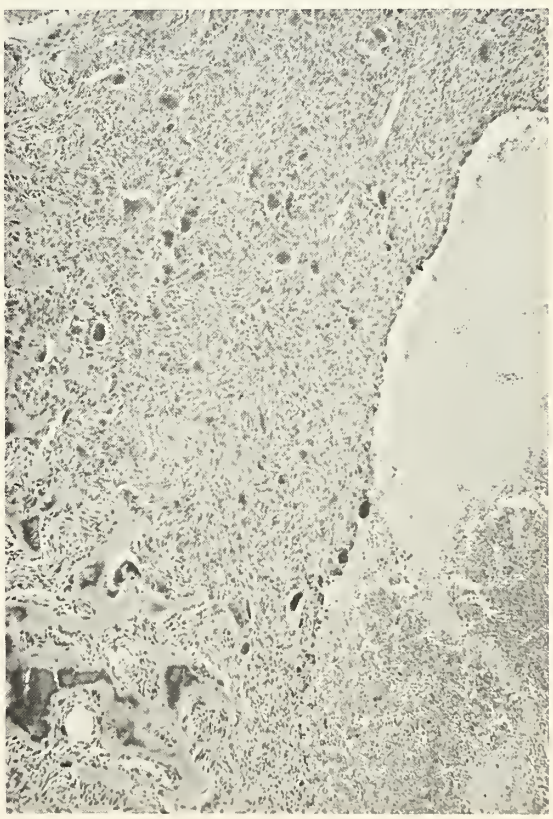

Figure 202
(Figures 202 and 203 are from the same patient)
GIANT CELL TUMOR OF THE LARYNX
A giant cell tumor of the larynx shows a large vascular-like cavity surrounded by a fibrous multinucleated giant cell and reactive bone histology. X63.

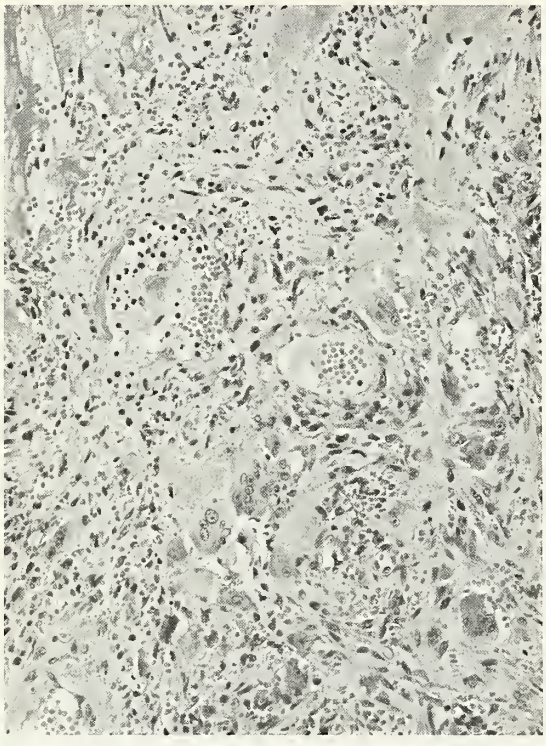

Figure 203
GIANT CELL TUMOR OF THE LARYNX
A higher magnification of the previous illustration supports the histology of the giant cell reparative granuloma. X160.

micromorphology was suggestive of the true giant cell tumor of bone in some cases, while others supported the histology of the central reparative giant cell granuloma of the facial bones.

INTRAOSSEOUS VASCULAR LESIONS

Site of Tumor. Intraosseous vascular lesions (nonaneurysmal bone cysts) show a predilection for the vertebrae and the skull. Extraspinal location is relatively rare, with the craniofacial bones, humerus, and digits being affected in descending order of frequency. Among the craniofacial bones, the skull, the mandible, and the maxilla are involved in descending order of frequency. In the skull, a frontal or parietal location predominates. Mandibular vascular tumors are reported in considerably greater numbers than those of the maxilla.

Incidence. There is nearly an equal sex distribution and, while the apparent incidence increases with age (after middle age), no age group is spared. Mandibular and maxillary vascular tumors tend to occur in younger subjects.

Clinical. Pericoronal bleeding with displacement of one or more teeth, swelling of the adjacent soft tissues, hyperthermia of the affected site, pain, or pulsating lesions can all be part of the symptom-sign complex associated with intraosseous tumors. In many patients, only a hard, nontender swelling that may have slowly enlarged over several months or years may be the only sign. Hemangiomatous lesions of the nasal bones present as an enlarging mass at the root of the nose. They are usually unilateral and a history of antecedent trauma is often elicited (Bridger).

Radiographic features are determined by the bone involved, rapidity of growth of the lesion, and histologic character of the tumor (Gamez-Araujo et al.), but all present as lytic lesions.

Gross. The gross appearance is as variable as the radiographic presentation and is one that ranges from a relatively circumscribed red-brown, 1 to 2 cm lesion, to a large, destructive, intraosseous blood-filled space.

Microscopic. Capillary, cavernous, or a mixed benign endothelial proliferation is seen microscopically. The cavernous forms may be indistinguishable from arteriovenous malformations. If the vessels are large (cavernous), the supporting stroma is minimal. A variably prominent stroma accompanies the capillary type. Malignant features are absent. Pressure atrophy of trabeculae and thinned,

expanded, and eroded cortices may be found.

Diagnosis. Even though histologically benign, vascular lesions of the gnathic bones are potentially lethal lesions that may be difficult to diagnose without exposing the patient to grave danger. This is particularly true for the large, cavernous types. Premature biopsy or extraction of teeth by an unsuspecting dentist can lead to extensive hemorrhage. Maxillary hemangiomas are considered to be more dangerous because of the variability of their radiographic appearance and greater difficulty in control of the hemorrhage. According to Kelly and associates, needle biopsy is considered wise and apparently does not lead to a hemorrhagic catastrophe.

Prognosis. The literature does not point to any significant prognostic differences in the behavior of a central hemangioma, either of the cavernous or capillary form. When the lesion is confined to bone and adequate surgical removal is performed, the prognosis is good. The treatment of choice is complete surgical eradication of the lesion. If cure is not jeopardized, cosmetic results are the second most important consideration.

The skull, mandible, and, especially, the maxilla are rare sites for a primary angiosarcoma of bone (Unni et al.).

OSTEOGENIC SARCOMA

Osteogenic sarcoma (osteosarcoma) is defined as a malignant neoplasm arising in bone or soft tissues in which the proliferating malignant cells produce osteoid substance. Osteoid, chondroid, or fibrous differentiation may predominate and thus yield osteoblastic, chondroblastic, and fibroblastic types of osteogenic sarcoma. By location, the osteogenic sarcomas are classically endosteal or medullary and then parosteal, periosteal, or extraosseous.

Frequency and Incidence. Although osteogenic sarcoma is the most common primary malignant tumor of bone, it is relatively rare in the oral and facial regions. The skull, jaws, and facial bones account for 6.5 percent of all osteogenic sarcomas, and in these upper respiratory areas the incidence has been roughly estimated as 0.07 per 100,000 per year for the United States population (Garrington et al.).

Osteogenic sarcomas of the long bones occur most frequently during the second decade of life, but in the skull and jawbones the highest incidence is reported in the third decade (excluding patients who develop osteosarcoma in Paget's disease of bone). In the pediatric age group, osteogenic sarcoma is the most frequent primary malignancy of the maxilla and mandible (Batsakis et al.). Males are afflicted more than females.

Most of the osteogenic sarcomas arise anew, but several conditions of bone have been associated with the subsequent development of osteogenic sarcoma. These include radiation (particularly prone are patients following radiation treatment for retinoblastoma), Paget's disease, and fibrous dysplasia (Unni and Dahlin).

Site of Tumor and Clinical Data. The mandible is affected more often than the maxilla, but it is the latter area of tumor growth that compromises the upper airway. In the facial bone area it is the maxilla that is most often the site of origin, followed by the bones of the maxillary and ethmoidal sinuses (LiVolsi).

The most common presenting symptom for osteogenic sarcoma of the facial bones is painful swelling. In the series presented by Caron and associates, almost half the patients with osteogenic sarcomas of the facial bones had extraction of teeth as their

"primary" treatment. The encroachment into the nasal cavity and paranasal sinuses yields signs and symptoms related to obstruction of those spaces.

The radiologic features of osteogenic sarcoma depend largely on the state of ossification and mineralization in the tumor (Finkelstein). There is, therefore, a wide variation of radiographic findings ranging from completely lytic to totally sclerotic. The majority fall somewhere between, with a mixture of both.

Gross and Microscopic. The gross appearance of osteogenic sarcoma is dependent upon the microscopic character, i.e., degree of osteoblastic, fibroblastic, or chondroblastic proliferation. Hence, the tumors may be firm, gritty, granular, fleshy, or fibrous (figs. 204-209).

The histologic appearance of osteogenic sarcomas of the skull and facial areas does not differ from that in the remainder of the body skeleton except that those involving the maxilla tend to be more vascular and fibrosarcomatous. For those desirous of an in-depth presentation of the histology of osteosarcoma, the Fascicle on Tumors of Bone and Cartilage by Spjut and associates is

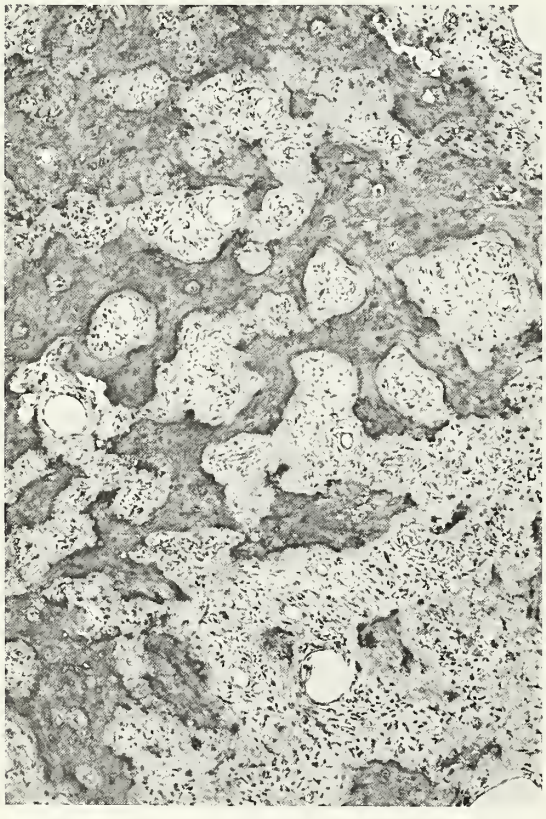

Figure 204
(Figures 204 and 205 are from the same patient)
OSTEOGENIC SARCOMA
Histology of a periosteal osteogenic sarcoma presents a rather heavily ossified lesion. X63.

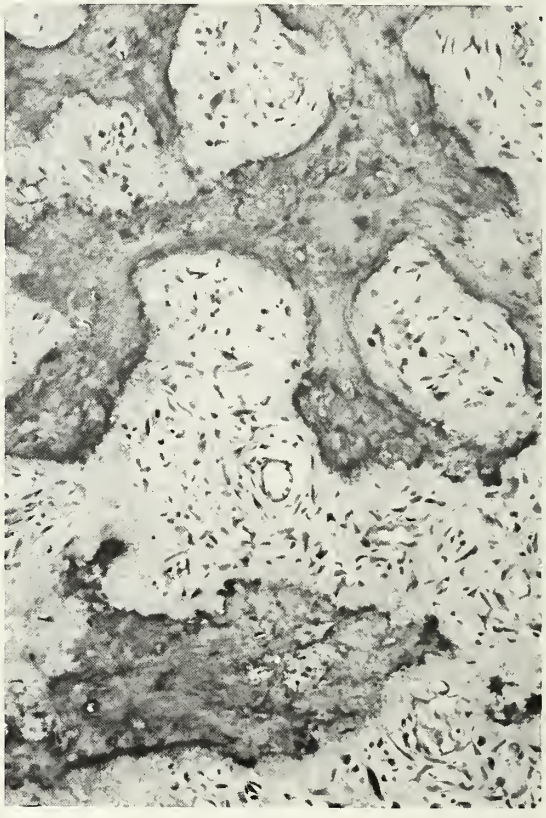

Figure 205
OSTEOGENIC SARCOMA
Note the bands of well formed osteoid and bone. The parosteal osteogenic sarcoma is typically well differentiated. X160.

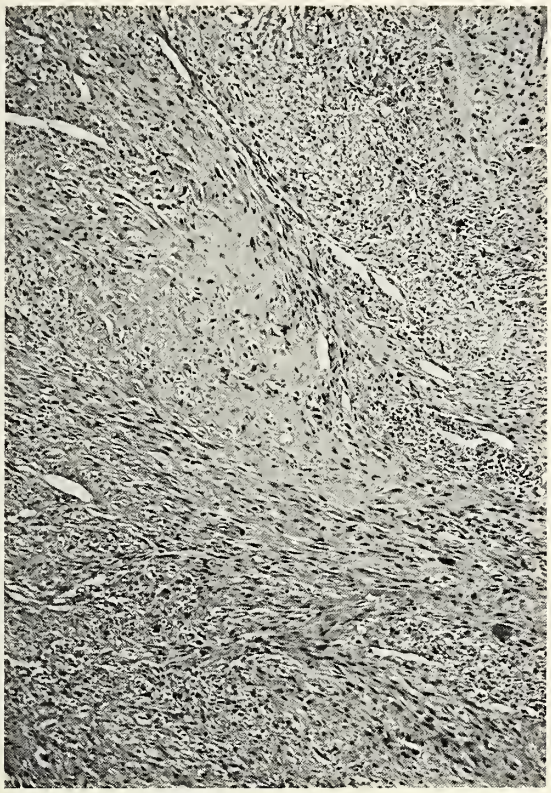

Figure 206
(Figures 206 and 207 are from the same patient)
OSTEOGENIC SARCOMA
Periosteal osteogenic sarcoma with lobulated islands of malignant cartilage and a spindled stroma area. X63.

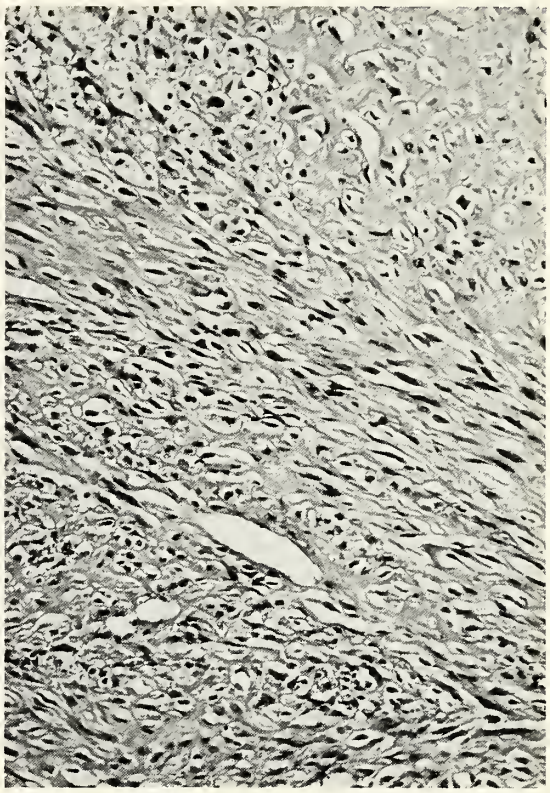

Figure 207
OSTEOGENIC SARCOMA
Trabecular mature osteoid and bone are not found, but the fine lacelike osteoid of osteogenic sarcoma are present in the predominantly chondroid lobules. X160.

recommended. This reference will also elaborate on the variety of osteosarcomas that can involve the bones of the skull and facial areas. A knowledge of these varieties is important because of their diverse prognosis.

Spread. Local recurrences and distant metastases are the bane of the surgeon attempting to salvage patients with osteogenic sarcoma of the bones of the skull and facial area. Recurrence, as expected, is more frequent with osteogenic sarcoma involving the maxilla, actually an 80 percent incidence in Caron's series. Recurrence appears usually within the first postoperative year. Distant metastases make their appearance over a varying period of time after primary treatment, but are usually manifest within two years. The lungs and brain are the most often involved sites of secondary deposits.

Distant metastases reduce ultimate survival to zero. If the sarcoma invades the nasal cavity and sinuses, the prognosis is also reduced to nearly nil, regardless of treatment (Fu and Perzin). Recurrences, while potentially dangerous for increasing the chances of distant metastases, are not fatal and they should be aggressively treated. If osteogenic sarcoma supervenes onto Paget's disease, there are few five-year survivors.

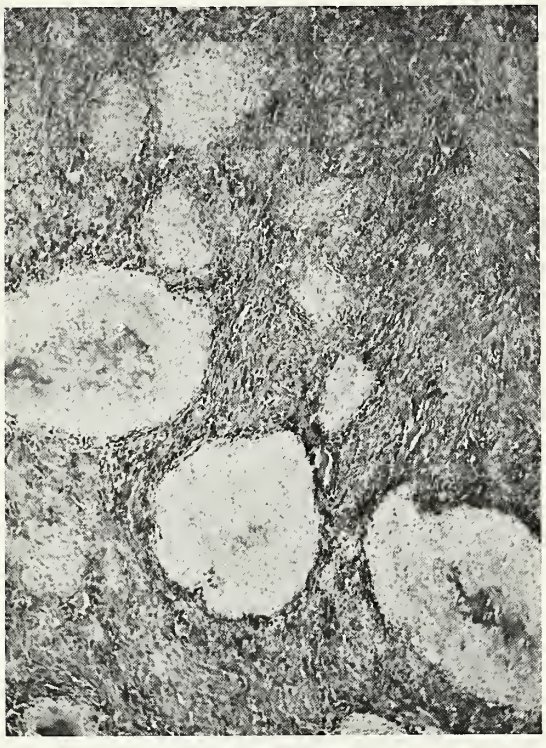

Figure 208
(Figures 208 and 209 are from the same patient)
OSTEOGENIC SARCOMA
This illustrates the intraosseous, well differentiated osteogenic sarcoma. There is fibroblastic proliferation lacking in conventional osteogenic sarcomas. There are disorganized areas of osteoid with little chondroid material. X63.

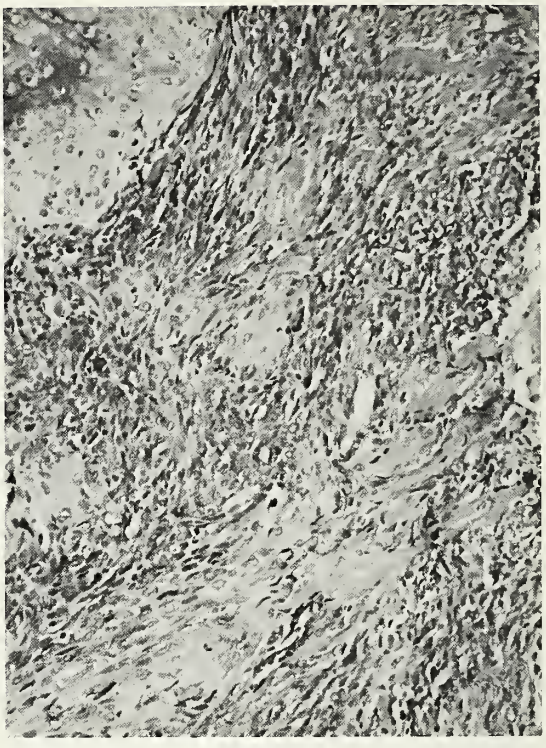

Figure 209
OSTEOGENIC SARCOMA
A higher magnification of the previous illustration. X160.

Treatment. The low survival rate of patients with conventional osteogenic sarcoma of the skull and facial bones has led to critical evaluation of modes of therapy. Experience with multimodal primary therapy for osteogenic sarcoma of this anatomic area is, at present, limited. But even the early apparent successes with such management of extra-facial osteogenic sarcomas is currently being re-examined. Late recurrence in patients who received postamputation drugs, decrease in disease-free survival with extended follow-up periods, and increase in long-term survival with surgical treatment alone are fostering new randomized trials (Batsakis et al.).

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CHORDOMA

Definition. Chordoma is defined as a malignant tumor characterized by a lobular arrangement of tissue which is usually composed of highly vacuolated cells (physaliphorous cells) and mucoid intercellular material. They are unusual dysontogenetic neoplasms that arise from remnants of the notochord.

Histogenesis and Pathogenesis. The distribution of almost 90 percent of chordomas at the upper and lower extremes of the vertebral column is strong circumstantial evidence that the tumors take their origin from ectopic chordal nodules rather than from remnants of the nucleus pulposus of the intervertebral discs (Binkhorst et al.).

Early in the third week of intrauterine life, the notochordal plate develops cranial to the primitive streak. During the fifth week, the notochord becomes enclosed within the bodies of the primitive vertebrae, passing through the mesenchyme which will form the atlas and odontoid process, and then enters the basiocciput. Passing through this structure for a short distance, it comes to lie directly in contact with the endoderm of the primitive pharynx (fig. 210). The notochordal tract commences in the sphenoid bone just posterior to the pituitary fossa, leaves the bone, and runs caudally along the central surface of the basisphenoid in close association to the pharynx, reenters the bone in

RELATION OF EMBRYONIC NOTOCHORD TO SURROUNDING STRUCTURES

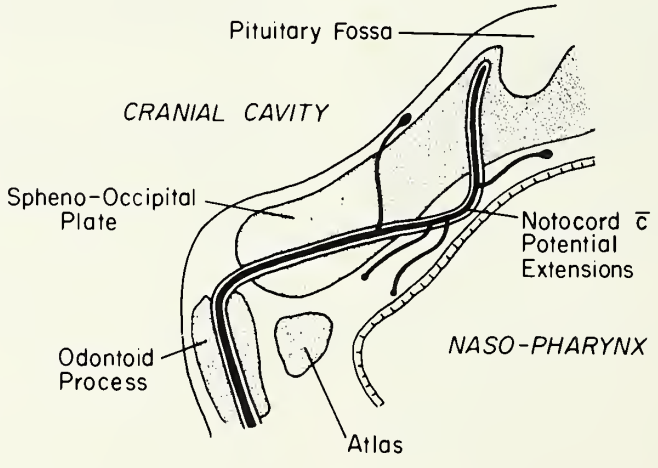

Figure 210
CHORDOMA
Schematic of the anatomic relationship of the notochord, suggesting areas of origin of chordoma from this structure.

the basiocciput, courses through the centers of the apical odontoid ligament, enters the odontoid process, and then down the center of the vertebral bodies to the coccyx.

As the vertebral bodies develop, the notochordal bar becomes divided into segments and normally disappears from the vertebral body, but persists in the nucleus pulposus of the intervertebral disc. During the eighth week of intrauterine development, myotomes and sclerotomes undergo descent and fusion to form permanent structures such as the musculature of the tongue and precursors of the basiocciput and basisphenoid. The notochordal cells degenerate where they are enclosed by cartilage or fibrocartilage. In areas where this cartilage or fibrocartilage is not totally encompassing, as in the areas where the notochordal rod lies free in its craniocervical course (the roof of the oral cavity just posterior to the hypophyseal pouch and adjacent to the foramen magnum and the odontoid process), the notochordal cells may fail to degenerate and persist. This persistence corresponds to the sites of occurrence of tumors of notochordal structure. In the craniocervical region, then, there are at least seven points of origin of the chordoma: dorsum sellae; Blumenbach's clivus; retropharyngeal notochordal vestiges; remnants in the apical ligaments of the dens; nuclei pulposi of cervical vertebrae; vestiges in the squama occipitalis; and ectopic localizations, such as the mandible and frontal sinus (Binkhorst et al.). Sensenig examined the notochord in a series of 266 embryos, ranging from 22 to 44 days gestation age, and found that the notochord came into contact with the pharyngeal epithelium at various points in over 50 percent of the embryos.

Age Distribution. The chordoma may be clinically manifest at nearly any age from childhood to late adult life. There is an apparent male predominance in a ratio of 3 to 1.

Early recognition of the tumor's presence is not the rule, but is more likely in the intracranial and upper cervical regions due to the limiting anatomic confinement. In this respect, Dahlin and MacCarty found an average age of 38 years for the sphenooccipital group and 58 years for the sacrococcygeal group.

Clinical Signs and Symptoms. These reflect the site of origin and extension (Table 15). Frequent initial complaints, however, in over 90 percent of the patients are visual in nature. These are in the form of diplopia or visual field defects. The diplopia is usually on the basis of sixth cranial nerve involvement. An intranasal mass resulting in a discharge and obstruction is also a common finding and, interestingly, is more common than signs and symptoms of pituitary gland involvement (Tarshis and Briant). Pain is common.

According to Wright, only a small proportion of craniocervical chordomas have a clinical presentation in the nasopharynx, and the

Table 15
CRANIOCERVICAL CHORDOMAS: PATTERNS OF EXTENSION

Site of Origin	Extensions
Dorsum sellae	Intrasellar Intracranial Intraorbit Nasopharyngeal
Clivus	Intracranial Nasopharyngeal
Retropharyngeal vestiges	Toward pharynx
Apical ligament of dens	Intracranial Nasopharyngeal
Nuclei pulpose	Intraspinal Intravertebral Prevertebral

majority of these will show evidence of intracranial involvement. The intracranial involvement signifies origin from that site. The low frequency of nasopharyngeal presentation claimed by Wright, however, is not the experience of others (Richter et al.). Over 90 percent of craniocervical chordomas studied by the authors clinically presented with a nasopharyngeal or intranasal mass.

Regardless of their location, the classic radiologic finding of a chordoma is an expansile osteolytic lesion with a soft tissue mass accompanying the bony lesion (Lim). Destructive changes in the clivus and adjacent structures are the dominant plain film findings. According to some authors, the above findings, accompanied by calcification, are said to be signs characteristic of clivus chordoma. The areas of bone erosion or osteolysis are projected in Table 15 for the different areas of origin. In some instances, prominent soft tissue masses are often clearly evident. The calcification present in chordomas is either due to dystrophic deposits of calcium within the neoplasm or the result of sequestration of bone fragments secondary to bone destruction. The calcification is most often nodular or a mixed nodular and cystic component and not unlike that seen in craniopharyngiomas, but it is typically retroclival or retrosellar in location (Batsakis and Kittleson; Lim).

A midline, avascular mass in relation to the clivus is seen on vertebral angiogram. The basilar artery is characteristically displaced superiorly and posteriorly with a prominent posterior convexity. If the chordoma remains confined within the clivus or if it extends mainly into the pharynx, little or no abnormalities on air studies are evident.

Gross. The chordoma is a gelatinous, lobulated, semitranslucent gray tumor. It appears partially encapsulated and possesses a pushing margin that Heffelfinger and associates claim "invites enucleation."

Microscopic. The typical chordoma (fig. 211) is pseudoencapsulated by fibrous connective tissue, which also divides the lesion into lobules. The lobules possess two characteristic appearances: sheets of cells or a pool of mucin. Each chordoma is capable of wide structural variations within itself. The least variable finding is the basic lobular pattern. The cellularity and cytomorphology vary according to the size, age, and location of the lobule. Infiltrative or peripheral nodules have a less mucoid matrix, better formed cells, and less intracellular vacuolation than do cells in the deeper parts of the neoplasm.

By light and electron microscopic evaluation, the chordoma is composed of variable numbers and proportions of three different cell types: stellate cells, intermediate cells, and physaliferous cells (Batsakis and Kittleson; Mikuz et al.).

The primary cells are oval or polygonal, and are often closely apposed to one another, appearing epithelial. Their cytoplasm is eosinophilic and granular or homogenous. Early vacuolar change may be seen in the cytoplasm. Vacuolation is a continuous process in the life of the cells and may be equated to an aging process, since stages can be followed from cell to cell until the typical physaliferous cell is achieved. Further progression of vacuolation produces a highly vacuolated syncytium in which cell outlines are destroyed. Usually, mitoses are infrequent and pleomorphism is not striking. If present, neither have prognostic significance.

Ultrastructural observations confirm the cell construction and destruction process given in the light microscopic description above (Kay and Schatzki).

Special mention must be made of a histologic variant of the craniocervical chordoma

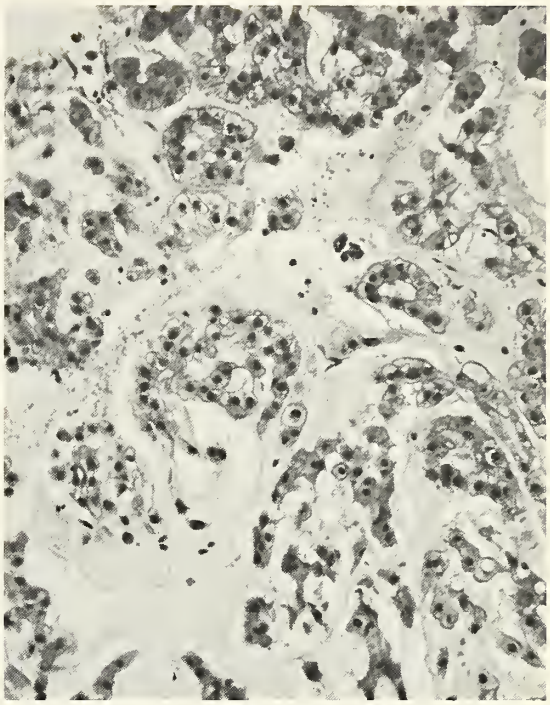

Figure 211
CHORDOMA
Note the multinucleated cells as well as the "soapbubble" physaliferous cells, characteristic of this tumor. X160.

— the chondroid chordoma (Richter et al.; Heffelfinger et al.). This lesion manifests features of chordoma and chondroma or chondrosarcoma in an admixture and of variable proportions. Its recognition is important because of an enhanced prognosis over nonchondroid chordomas.

Treatment. Complete surgical removal offers the best chance for cure, but is rarely achieved in the craniocervical region. Because of the friability of the tumor and the anatomic location, spillage and implantation during operative resection is very likely and, hence, recurrences occur. Because of the usual slow growth of the neoplasm, prolongation of life, not cure, may be achievable by combination therapy that includes postoperative irradiation (Tewfik et al.).

Prognosis. The typical (nonchondroid) chordoma of the craniocervical region does not carry a good prognosis. It is usually far advanced when discovered, and the cranial nerves at the base of the skull are subject to involvement as the tumor expands. Chordomas may cause death within a short time or may be protracted over an interval of one or two decades with multiple procedures for the persistence of tumors. Approximately 80 percent of the patients with cervical chordoma die within the first five years. A search of the literature has not revealed a single patient who had remained free of tumors over 20 years. Metastases from the craniocervical tumors are rare, but have been documented (Batsakis and Kittleson).

Heffelfinger and associates' study suggests a considerable difference between the typical spheno-occipital chordoma and the chondroid chordoma — an average survival time for 19 patients with chondroid chordomas of 15.8 years as compared to 4.1 years for 36 patients with typical chordomas. This difference exists despite similar treatment programs.

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EOSINOPHILIC GRANULOMA

SYNONYMS AND RELATED TERMS: Histiocytosis X; nonlipid histiocytosis.

Definition. Eosinophilic granuloma is a nonneoplastic lesion of unknown etiology, characterized by an intense proliferation of reticulohistiocytic elements with varying numbers of eosinophilic leukocytes, lymphocytes, plasma cells, and multinucleated giant cells.

Much confusion exists as to whether this entity of eosinophilic granuloma is a separate entity of bone or whether it is a localized osseous manifestation of the histiocytosis "X" of Lichtenstein, which also includes the Hand-Christian-Schuller and Letterer-Siwe diseases, a more disseminated and possibly fatal osseous and soft tissue disease processes. Perhaps the otolaryngologist and pathologist should think of the eosinophilic granuloma, or the histiocytosis "X" as: (1) a disease characterized by general infiltration of the reticuloendothelial system and other tissues by histiocytes, a short clinical course, and poor prognosis (type I); and (2) a disease type characterized by variegated lesions, mainly osseous, often solitary, but sometimes multicentric, infiltrated by histiocytes mixed with eosinophils, a protracted course, and a generally favorable prognosis (type II) (Schuknecht and Papaspyrou). The former can, and probably will, involve the head and neck along with its systematic manifestations, but it is the latter type that will have unifocal, sometimes multifocal, lesions involving most often the skull and, particularly, the temporal bone.

Incidence, Age, and Sex. Of 25 patients with eosinophilic granuloma of the skull or temporal bone presented by Appling and associates, 16 were males. This ratio is similar to other series (Cinberg; McCaffrey and McDonald; Sweet et al.). The disease affects caucasians more frequently than blacks (Cinberg). Age at presentation (Appling et al.) ranged from 18 months to 31 years, with 18 patients being 10 years old or younger). Twenty-two patients presented initially with unifocal lesions, but 7 eventually developed multifocal disease over a period of time that varied from one to five months after initial diagnosis. Of 6 patients with lesions involving the temporal bone, only 1 was unifocal.

Clinical. Patients with diffuse type I disease, usually infants or young children (or rarely an adult), will present with an acute, rapidly progressive, systemic illness, with symptoms such as intractable otitis media, osseous defects (especially in the skull), lymphadenopathy, skin lesions, diabetes insipidus, or with a lytic lesion in a bone or a single infiltrative lesion in the viscera.

In a study of 22 patients with temporal bone disease, McCaffrey and McDonald note aural discharge as the presenting symptom in 10, which increased to 15 patients during the course of the disease. The next most common symptom was swelling in the temporal bone area in 9 patients. In 7 patients, all symptoms were limited to the temporal bone, while in others, nonotologic symptoms were bone pain, skin lesions, polyuria-polydipsia, fever, weight loss, lymphadenopathy, and exophthalmos.

Physical examination revealed otitis media in 59 percent of the patients, most likely a suppurative type, although occasionally granulation tissue or an aural polyp was noted. External otitis occurred in almost half the patients. The localized eosinophilic

granuloma in the temporal bone may break through the bony walls into the middle or external ear, producing an aural discharge. Mastoid destruction was noted in 9 of the 22 patients. Hearing loss and vertigo were infrequent occurrences. Extra-ototic clinical findings in the order of decreasing frequency were oral lesions, skin lesions, pulmonary infiltrate, cervical lymphadenopathy, and diabetes insipidus.

Gross. The tissue is soft, faintly yellow to red-brown, and may contain areas of necrosis or hemorrhage.

Microscopic. The predominant finding is moderately large reticulum cells that contain rounded, vesicular, often indented nucleus with a small centrally placed nucleolus (Appling et al.). The cytoplasm varies in amount and is slightly granular and eosinophilic (figs. 212, 213). Multinucleated giant cells may be seen. Eosinophils may be scarce. There seems to be a suggested correlation with prognosis and the number of eosinophils present with the histiocytic element. The more the eosinophils, the better the prognosis.

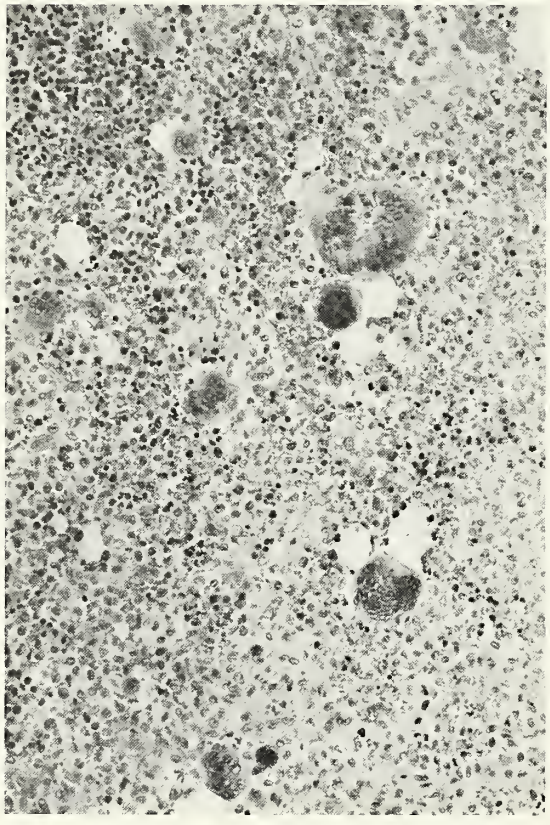

Figure 212
EOSINOPHILIC GRANULOMA
An eosinophilic granuloma of the temporal bone presenting as a single osteolytic lesion compound of histiocytes, multinucleated giant cells, and an eosinophilic leukocyte infiltrate. X160.

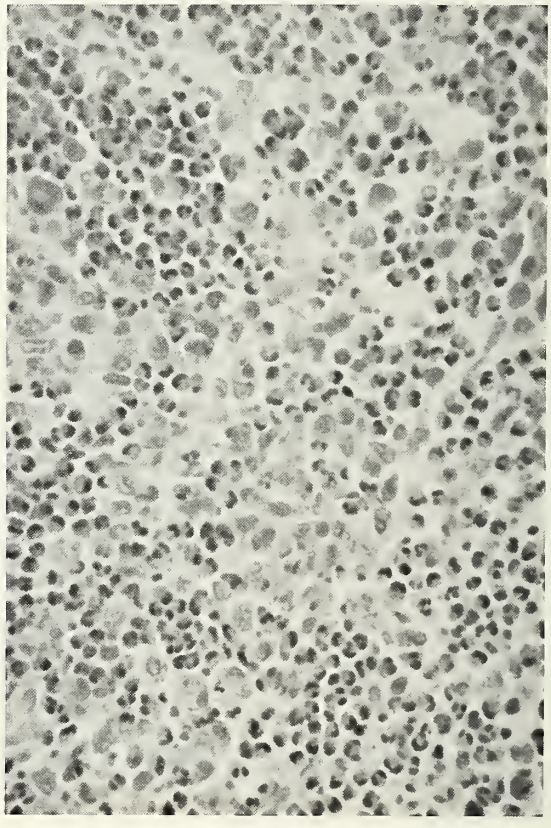

Figure 213
EOSINOPHILIC GRANULOMA
This eosinophilic granuloma of the temporal bone emphasizes the numerous eosinophilic leukocytic cells among the histiocytes. X400.

Electron microscopic studies reveal granules within the cytoplasm of the histiocytes, similar to structures seen in Langerhans' cells in normal skin.

Differential Diagnosis. Any destructive inflammation of the head and neck area, particularly in the skeletal elements, such as tuberculosis, syphilis, and osteomyelitis, must be ruled out. Cholesteatoma and neoplasia of the bones, such as fibrous dysplasia and giant cell tumor, all can be confused with the clinical picture of eosinophilic granuloma. More important, however, is to be able to possess a high index of suspicion of the possibility of eosinophilic granuloma when the entity presents as external otitis, aural polyps, acute mastoiditis, or chronic suppurative otitis media.

Treatment and Prognosis. Therapeutic approaches include surgery, radiation therapy, and chemotherapy, either individually or in combination. For a local unifocal lesion, attempted conservative excision or debulking and preservation of vital structures within the temporal bone seems advisable. Low dose radiotherapy has been administered separately or in combination with surgery in the localized tumor. Chemotherapy appears best suited to multifocal diseases. Observation of a local tumor that has been established as a unifocal lesion has revealed spontaneous remission.

With unifocal eosinophilic granuloma in the skull or temporal bone, the prognosis of patients is quite good, but becomes less so when the disease recurs or is recognized as part of a multifocal process (Appling et al.). Dissemination of an initial solitary lesion usually occurs before the age of five years and within the first six months of the illness. If a new bone lesion fails to appear after 12 months, one may anticipate a cure. In multifocal disease, the chance of survival is enhanced when the age of onset is later, when no (or few) viscera are involved, and when numerous eosinophils are found. The mortality rate is 77 percent in neonates. In patients with bone involvement and more than four visceral lesions or with more than four visceral lesions without bone involvement, the prognosis is especially poor; however, patients with involvement of multiple bones and no visceral lesions usually survive, but with prolonged morbidity.

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HAMARTOMAS, TERATOID TUMORS, AND TERATOMAS

HAMARTOMAS

Hamartomas in the upper respiratory tract are simple congenital malformations composed exclusively of components derivable from tissues indigenous to the area (figs. 214, 215). They are spontaneous growths which produce a mixture of cellular elements in excess of that normally seen. In many cases, the lesions seem to represent an exaggeration of a normal physiologic process. The lesions are usually self-limiting.

In the above sense, congenital lipomas, tuberous sclerosis and its congeners, multiple enchondroses and exostoses, and neurofibromas may be regarded as hamartomas.

Cartilaginous hamartomas, containing other mesodermal components and epithelium such as is found in the trachea and lungs, are exceedingly rare in the larynx and paranasal sinuses (Majumder et al.). Glandular hamartomas also are unusual airway lesions (Baillie and Batsakis).

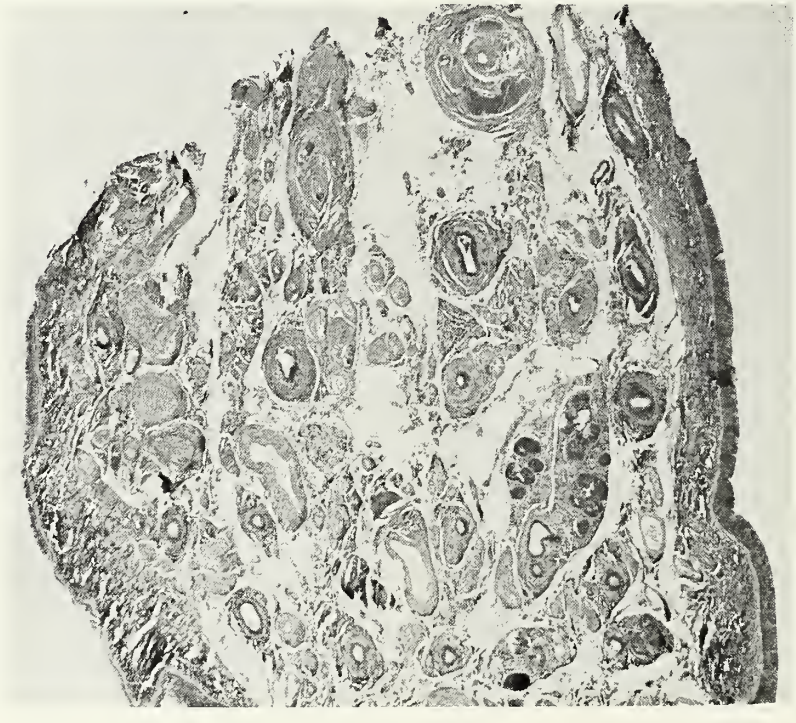

Figure 214
(Figures 214 and 215 are from the same patient)
HAMARTOMA
A hamartoma of the larynx, characterized by glandular and vascular proliferation with a particularly prominent smooth muscle band surrounding the vessels and, apparently, the glandular structures. X25.

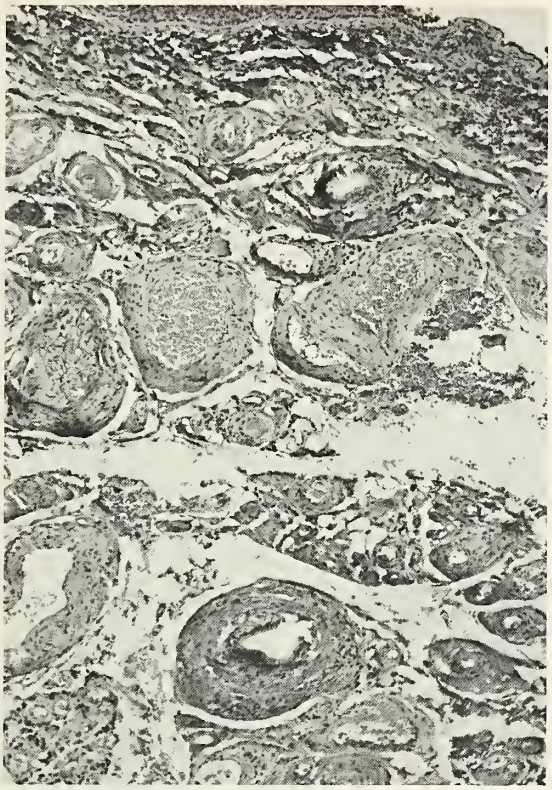

Figure 215
HAMARTOMA
Higher magnification of the previous illustration emphasizes the benign histology of the proliferating structures. X63.

In contrast to hamartoma, there is choristoma, which is defined as a simple congenital malformation composed exclusively of tissue components derivable from tissues not indigenous to the area. In the AFIP-OTR experience, these types of tumors have occurred in the middle ear and in the soft tissue of the neck.

TERATOID TUMORS

The term "teratoid" is used by us in a generic sense to signify tumor-like growths that are composed of tissue derivatives of one or more germinal layers. Unlike teratomas, they are not true neoplasms and their genesis is from congenital inclusions. They most often present as dermoid cysts. McAvoy and Zuckerbraun have divided the cysts into several clinical groups. Group 1 cysts are located in the periorbital region and are thought to occur as inclusions between the maxillary and mandibular processes in the naso-optic groove or pit. Depending on the depth of the inclusions, these cysts can appear in the retro-orbital, supraorbital, or canthal regions. Group 2 lesions are those found overlying the dorsum of the nose and are thought to arise from inclusions at the time of ossification of the frontonasal plate. Group 3 cysts are those found in the submental region, floor of mouth, and the region of fusion of the first and second branchial arches in the midline. These cystic lesions can assume major clinical importance because of their size and can interfere with the airway. Group 4 lesions are formed at the mid-ventral and mid-dorsal fusion in the suprasternal, thyroidal, and suboccipital regions, where they may be confused with thyroglossal duct cysts or other thyroid lesions.

Dermoid Cysts of the Nasal Region

These cysts present a rather distinct aggregation of characteristic clinical features. Nasal dermoid cysts often are apparent shortly after birth, most often as a small midline pit or depression on the bridge of the nose from which hairs may protrude. The pit represents the opening of a sinus tract that may extend between the nasal bones to the cribriform plate or into the nasal septum.

Varieties. The cysts can be differentiated according to their location into superficial and deep (septal) cysts. Perhaps these cystic lesions would fit into the Group 2 lesions described above by McAvoy and Zuckerbraun. The superficial cysts are located in the region of the perpendicular plate of the

ethmoid bone and the quadrangular cartilage, while deeper cysts may be found within the columella and in the verner. Sometimes the cysts may have a dumbbell configuration, with one part of the cyst above the other below the suture line of the nasal bones.

Incidence. Approximately half the reported nasal dermoids are recognized at birth, but the average age of patients at the time of surgical treatment is 11 or 12 years. There is a slight male predominance.

Clinical. Cysts in this region, aside from a gradual growth, usually cause no discomfort. The majority, however, become infected.

Gross. The size of a dermoid cyst is variable, ranging from a few millimeters to several centimeters in diameter (fig. 216).

Microscopic. The walls are often thick and fibrotic and lined with squamous epithelium

Figure 216
DERMOID CYST
In this dermoid cyst, removed from the midline external nose area, the ectodermal contents of the tumor are obvious.

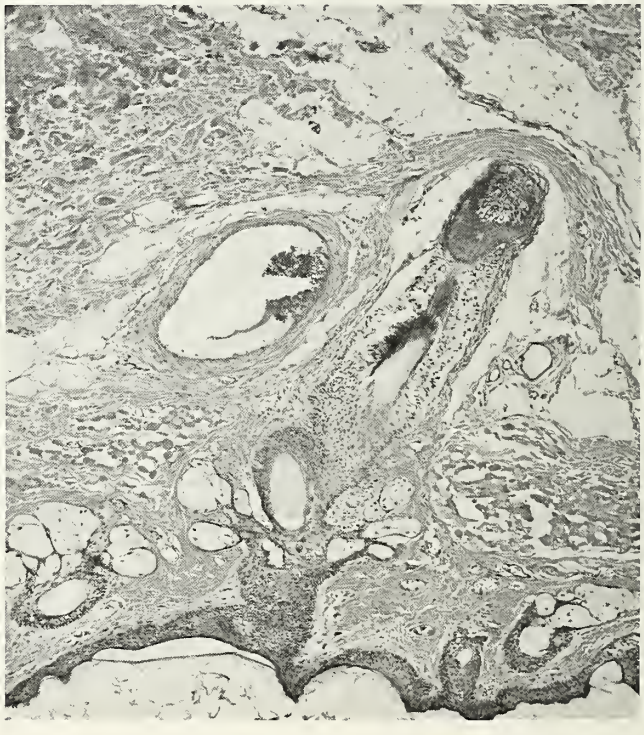

Figure 217
DERMOID CYST
Microscopic view of a dermoid cyst reveals the benign keratinizing squamous cell lining and the underlying adnexal structures. X63.

that resembles skin, and contains hair follicles and sebaceous glands. (fig. 217). The cavities of the cysts are filled with a greasy grumous material. Hair may also be present.

Treatment. Dermoid cysts are treated by surgical excision. Recurrences are directly related to the accessibility of the cyst. In recurring lesions, complete dissection of the epithelial lining may be difficult. Such recurrences are less likely if the lining is destroyed by electrocoagulation.

"Hairy Polyps"

Extranasal teratoid lesions of the upper airway appear to have a sharp localization to the nasopharynx and the soft palate. They may also occur in the area of the infundibulum and sella turcica.

In the nasopharynx and oropharynx, such teratoid lesions have been called "hairy polyps."

Hairy polyps are commonly recognized at birth or shortly thereafter. They occur predominantly in girls. They may escape early recognition due to small size or lack of symptoms; they are detected incidentally during routine examination.

Approximately 60 percent originate in the nasopharynx and others in the tonsil region and oropharynx. They are frequently pedunculated with the pedicle attached to the lateral nasopharyngeal wall or on the nasopharyngeal aspect of the soft palate. They occur singly.

Clinical. Signs and symptoms depend upon the size and location of the lesions and include dyspnea, dysphagia, cough and cyanosis, or complete nasopharyngeal obstruction. Hairy polyps are rarely associated with other congenital malformations.

Gross. The hairy polyps have been described as having various shapes (club, sausage, pear, thumblike). They are usually gray or white, and have the appearance of skin. In some cases, the proximal part of the pedicle is covered with mucosa. Their size ranges from 0.5 to 6.0 cm.

Microscopic. In addition to skin and its appendages, the lesions contain fibroadipose tissue, fibrovascular connective tissue, smooth and striated muscle, glandular tissue, cartilage, and bone (fig. 218).

Treatment. Treatment is conservative surgical excision. There is no malignant potential (Chaudhry et al.).

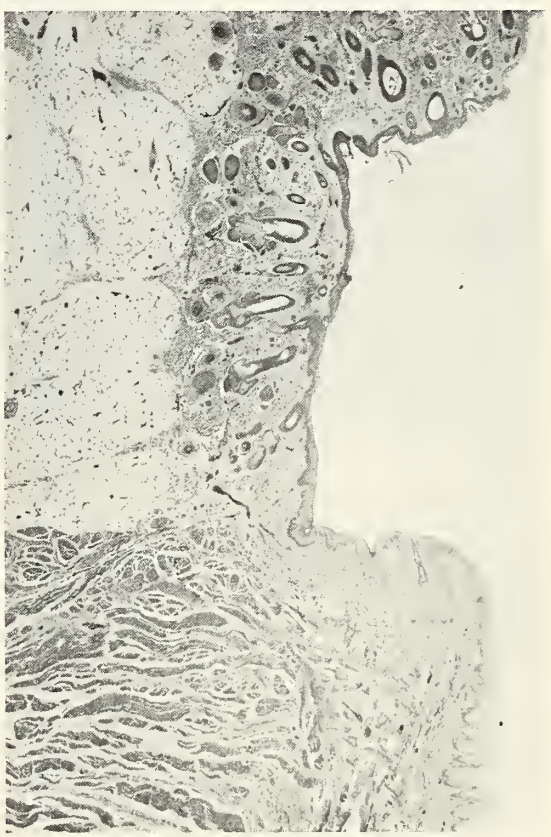

Figure 218
"HAIRY POLYP"
A histology of the so-called hairy polyp of the nasopharynx reveals a normal skinlike surface with underlying adnexa, but with the addition of adipose and muscle tissue. X25.

TERATOMAS

Sites of Tumor. The neck and the nasopharynx are the most common sites of teratomas in the head and neck. Nearly 100 examples have been reported from each area. In these sites and particularly in the nasopharynx, the true teratoma is to be distinguished from the dermoid (hairy polyp) that arises from an inclusion error during embryonic life (Batsakis).

Pathogenesis. Teratomas of this region, like those of the sacrococcygeal region and chest, very likely arise from embryonic tissue about the primitive streak and notochord after an escape from external governing influence (Damjonov and Solter).

In teratomas, there are anomalies both at the level of differentiation and also of the type of differentiation. A low level of differentiation with a concentration of cells on a replicative rather than functional activity is seen in the malignant variant of teratoma.

Clinical. In the neck, like their counterparts elsewhere, teratomas occur in two distinct clinicopathologic settings (Kemp). They are most commonly found in the fetus in utero or in the newborn. Hydramnios, stillbirth, premature or obstructed labor, and respiratory tract obstruction in the neonate are frequent accompaniments. In this age group, the teratomas are nearly always histologically benign, usually asymmetrical, and commonly occupy the whole of the neck on one side.

A proportionately much smaller number of teratomas of the neck are present in adult life. Here, the tumors manifest a distinctly different biologic course and have a high incidence of malignancy (Batsakis).

Almost all the reported cases of benign cervical teratomas have been detected clinically before the age of 1 year; 80 percent are present at birth, and nearly 20 percent are in stillborns. The age of presentation with adult cervical teratomas has ranged from 23 to 85 years. In both age groups, the sexes have been equally represented.

Microscopic. In the nasopharynx and paranasal sinuses, teratomas have been almost exclusively well differentiated, composed largely of neuroectodermal derivatives, and have presented in infants and children (figs. 219, 220). They contain mature as well as immature tissues. The latter are most often neural in type, on occasion resembling differentiating neuroblasts. The presence of such

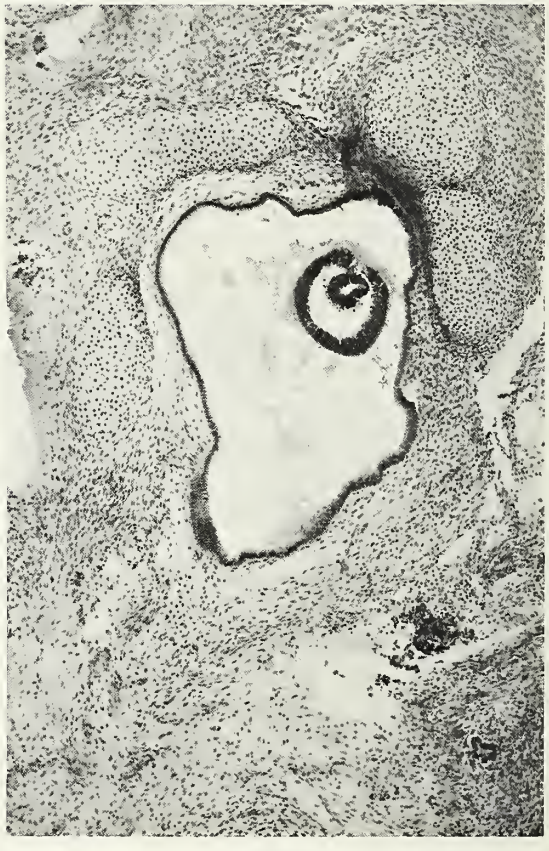

Figure 219
(Figures 219 and 220 are from the same patient)
TERATOMA
A teratoma of the nasopharynx in a newborn infant reveals the benign tissue representing mesenchymal, entodermal, and ectodermal elements. X63.

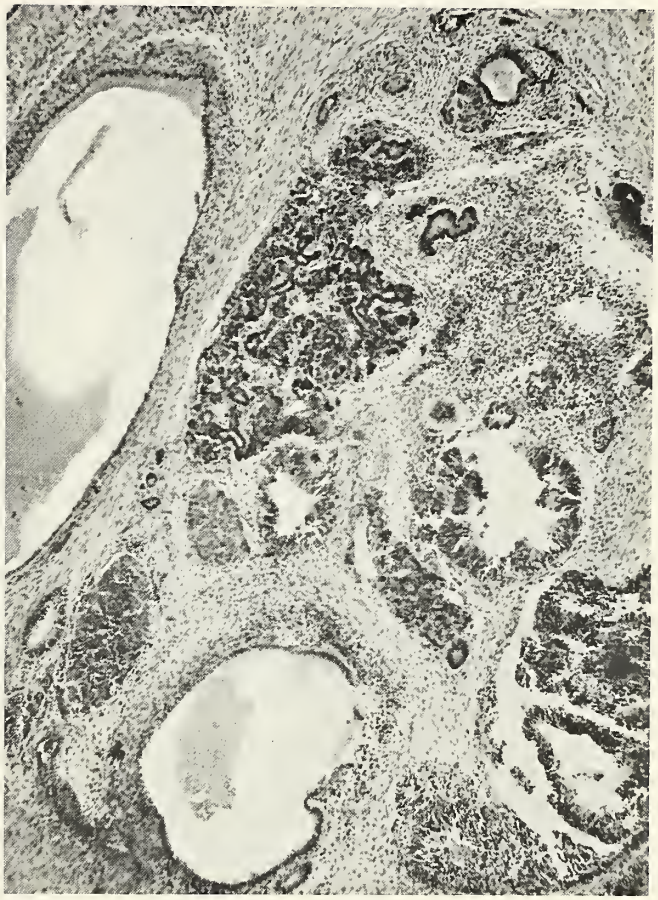

Figure 220
TERATOMA
This view of the neoplasm in figure 219 shows glandular tissue elements predominating. X63.

immature tissue in an otherwise benign teratoma is of little prognostic significance. If removable, these teratomas rarely recur whether or not they contain immature areas.

The malignant teratomas of the nasopharynx and paranasal sinuses are, in effect, teratocarcinomas. The malignant elements conform to those found in malignant teratomas of extracervical sites in childhood in that an undifferentiated epithelial or neuroepithelial malignancy is found. Dicke and Gates have presented a patient and reviewed the preceding literature. The teratocarcinoma occurs in young and middle-aged adults, contains an admixture of all three given layers (figs. 221, 222) and manifests an aggressive local infiltration without metastases. Death is due to intracranial extension.

Heffner and Hyams have investigated 20 patients with sinonasal tract neoplasms having the combined histologic features of carcinosarcoma and teratoma which they designated teratocarcinosarcoma. The patients contained in the AFIP-OTR material were adults with an age range from 18 to 79 years (median age, 60 years). The neoplastic entity was clearly malignant, with 60 percent of the patients not surviving beyond three

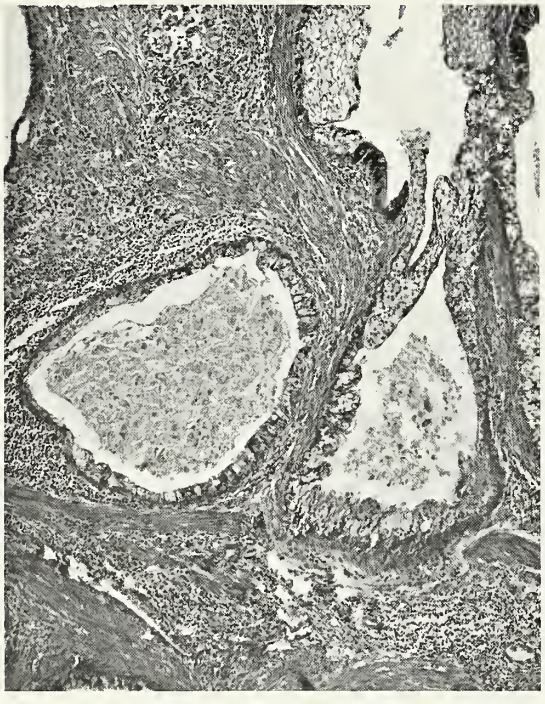

Figure 221
(Figures 221 and 222 are from the same patient)
MALIGNANT TERATOMA
A malignant teratoma which involved the sinonasal tract. Squamous epithelial and columnar epithelial-lined cysts are detectable. X25.

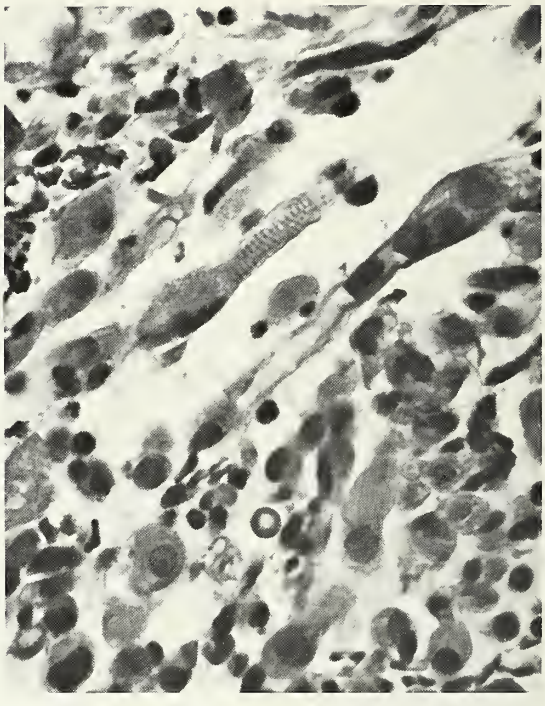

Figure 222
MALIGNANT TERATOMA
An area of rhabdomyosarcoma in the sinonasal tract neoplasm shown in figure 221. X400.

years (average survival, 1.7 years) following diagnosis regardless of the type of therapy. Aggressive therapy (combined surgery and irradiation) seems justified since 40 percent of the patients so treated survived three years or longer with no current evidence of neoplasm (average followup time, 6.1 years).

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LYMPHORETICULAR TISSUE NEOPLASIA

LYMPHOMA

Definition. In this Fascicle, the term lymphoma will be applied to primary malignant tumors of reticular tissue that are composed of primitive reticular cells, their histiocytic or lymphocytic derivatives, or combinations of these cell types.

From a practical standpoint, the pathologists who examine a biopsy specimen of the upper respiratory tract feel quite satisfied if they can be certain of the diagnosis of lymphoma. This is in view of the usually small size of the biopsy specimen, the possible distortion due to the biopsy instrumentation, and, particularly, if a frozen section is required. This latter procedure is rarely if ever justified and causes serious artifact in the later permanent histologic section.

It is not the purpose of this Fascicle to settle the controversy of the classification of the neoplasms of the lymphoid tissue, particularly the non-Hodgkin's lymphoma. Recently there has been a deluge of information regarding the immunologic and morphologic correlation of the numerous classifications of the non-Hodgkin's lymphoma (Nathwani). There is also a recent attempt at a new formulation of non-Hodgkin's lymphoma which is based on cytology alone (Krueger et al.) and not requiring special tissue preparation and laboratory technics. It does compare favorably with the time-tested Rappaport classification. An appropriate approach at this writing would be to utilize a modified classification of the World Health Organization typing of Neoplastic Disease of Haematopoietic and Lymphoid tissue (Table 16) by Mathe and Rappaport.

NON-HODGKIN'S LYMPHOMA

In this group is included nodular lymphosarcoma, diffuse lymphosarcoma, reticulosarcoma, and unclassified malignant lymphomas as they affect the upper respiratory tract (figs. 223, 224).

Table 16

MODIFIED CLASSIFICATION OF HISTOLOGIC AND CYTOLOGIC TYPING OF NEOPLASTIC DISEASE OF HAEMATOPOIETIC AND LYMPHOID TISSUE
International Histological Classification of Tumours, World Health Organization

LYMPHOSARCOMA	**RETICULOSARCOMA**
Nodular lymphosarcoma	**UNCLASSIFIED MALIGNANT LYMPHOMA**
Diffuse lymphosarcoma	**HODGKIN'S DISEASE**
Lymphocytic	with lymphocytic predominance
Lymphoplasmacytic	with nodular sclerosis
Prolymphocytic	with mixed cellularity
Lymphoblastic	with lymphocytic depletion
Immunoblastic	**PLASMACYTOMA**
Burkitt's tumor	

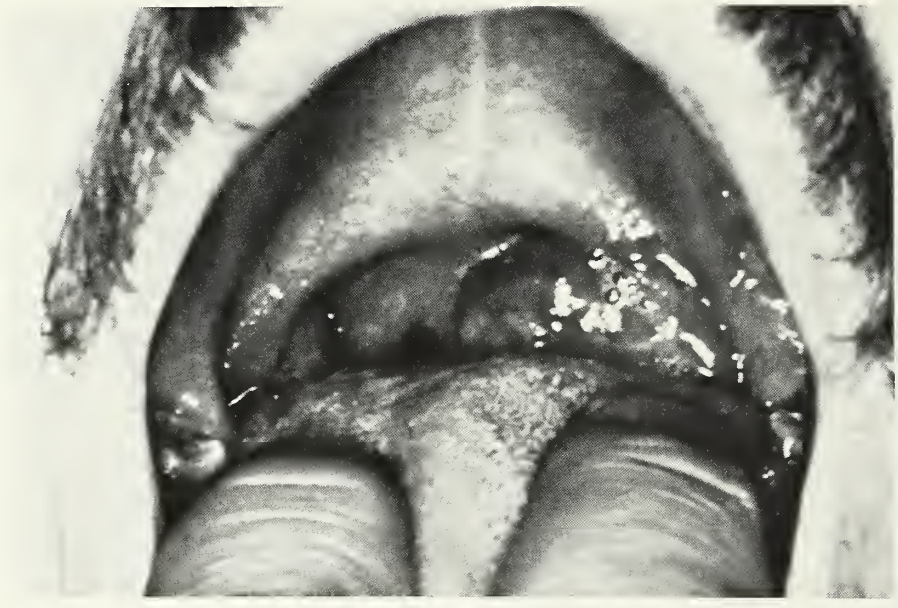

Figure 223
NON-HODGKIN'S LYMPHOMA
This clinical view shows bilateral involvement of the palatine tonsils by non-Hodgkin's lymphoma in a 42 year old man.

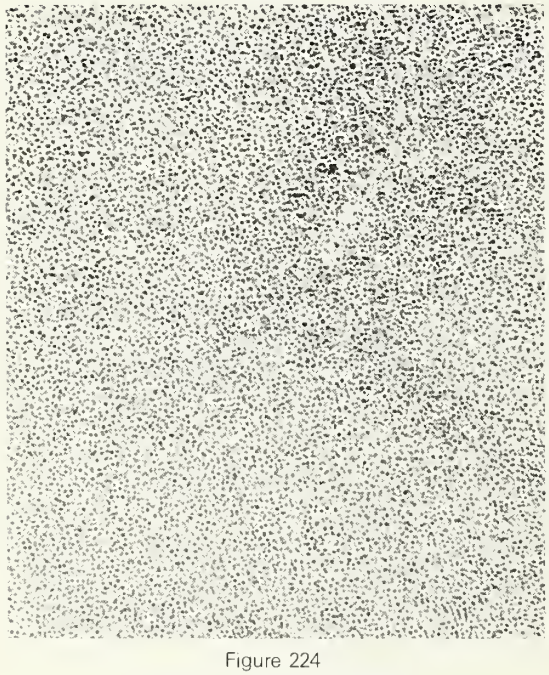

Figure 224
NODULAR LYMPHOSARCOMA
A nodular lymphosarcoma of the palatine tonsil with a well differentiated histology. X63.

Incidence. Incidence of non-Hodgkin's lymphoma and Hodgkin's disease of the various anatomic sites of the upper respiratory tract and ear listed in the AFIP-OTR is seen in Table 17. A 10-year survey of the sinonasal tract, pharynx, and tonsil, and its involvement with non-Hodgkin's lymphoma from the AFIP-OTR is presented in Table 18. The greatest incidence of non-Hodgkin's lymphoma involves the palatine tonsil, followed by the combined nasal cavity and paranasal sinuses, and then the nasopharynx.

Table 19 contains the age and sex incidence of the different types of upper respiratory tract non-Hodgkin's lymphoma contained in the AFIP-OTR. While the age range of other forms is wide, nodular lymphoma is confined to the older age group. Burkitt's lymphoma (fig. 225) is essentially confined to children. Reticulosarcoma (figs. 226-228) reveals a much higher prevalence in males.

Table 17

INCIDENCE OF LYMPHOMA IN THE UPPER RESPIRATORY TRACT AND EAR
AFIP Otolaryngic Tumor Registry

Site	No. Cases	Non-Hodgkin's Lymphoma	Hodgkin's Lymphoma
Nasopharynx (1945-70)	1487	50 (3%)	10 (.6%)
Pharynx (1945-70)	1328	19 (1.4%)	4 (.4%)
Tonsils (1945-76)	1916	220 (11%)	30 (1.5%)
Nasal Cavity (1969-73)	457	5 (1.1%)	1 (.2%)
Sinuses (1969-73)	149	6 (4%)	—
Larynx (1945-75)	7900	13 (.2%)	4 (.05%)
External ear (1945-75)	1379	1 (.07%)	—
Middle ear (1945-75)	260	2 (.8%)	—

Table 18

INCIDENCE OF NON-HODGKIN'S LYMPHOMA BY SITE AND TUMOR TYPE
AFIP Otolaryngic Tumor Registry (1966-1977)

Tumor Type	Nasal Cavity and Paranasal Sinuses	Nasopharynx	Palatine Tonsils Vallecula	Total
Nodular lymphosarcoma	1	2	3	5
Diffuse lymphosarcoma				
Lymphocytic	1	1	2	4
Lymphoplasmacytic	—	—	—	—
Prolymphocytic	4	2	6	12
Lymphoblastic	5	2	10	17
Immunoblastic	—	—	—	—
Burkitt's tumor	—	1	2	3
Reticulosarcoma	4	2	11	17
Unclassified	1	—	—	1

Gross. Various presentations of non-Hodgkin's lymphoma are to be expected in the complex anatomic areas of the upper respiratory tract. Early in the disease, a red mass (possibly polypoid) is usually noted, except in the palatine tonsils where prominent unilateral or bilateral diffuse enlargement is common (fig. 223). Ulceration and necrosis may accompany the findings, particularly in long-standing cases. Local infiltration, usually into adjacent bony tissues, can occur early or late in the disease. The cut surfaces of the neoplasm, probably better emphasized in the palatine tonsils, is a "fish flesh" gray-white, uniform, glistening, slightly bulging convex surface with obliteration of normal organ landmarks, such as crypts. Necrosis and inflammation will alter this picture.

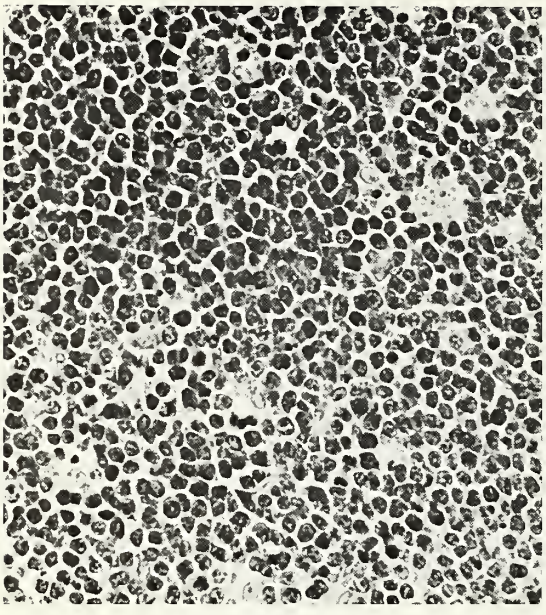

Figure 225
BURKITT'S TUMOR
In this Burkitt's tumor of the African type, the phagocytic histiocytes are prominent. X250.

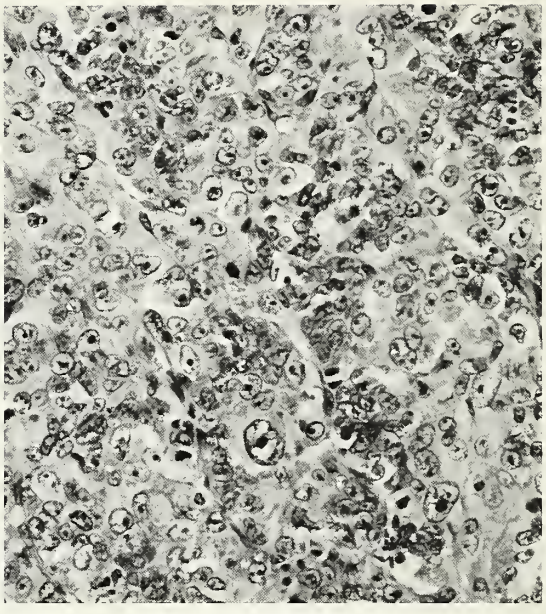

Figure 226
RETICULOSARCOMA
This reticulosarcoma occurred as a destructive mass of the sinonasal tract. X400.

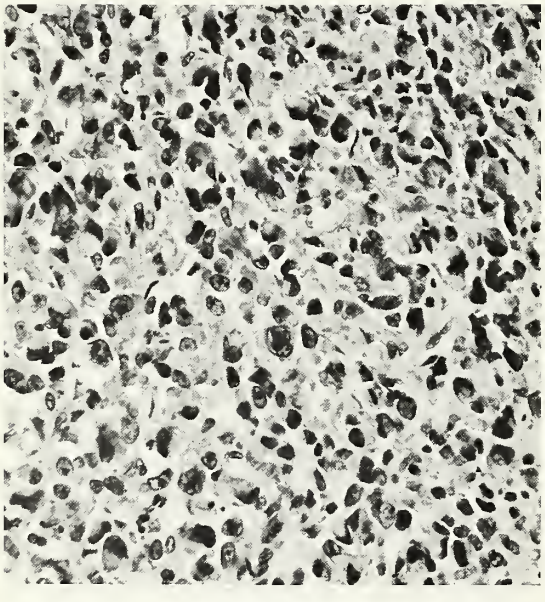

Figure 227
(Figures 227 and 228 are from the same patient)
RETICULOSARCOMA
This undifferentiated neoplastic process from the nasopharynx was considered a reticulosarcoma with a combination of undifferentiated and histiocytic cells. X400.

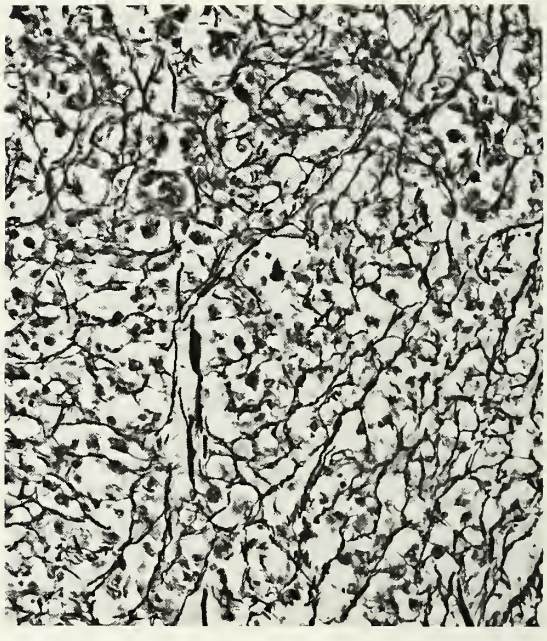

Figure 228
RETICULOSARCOMA
A reticulum stain reveals marked positivity, a finding supporting the diagnosis of reticulosarcoma. X400.

Table 19

AGE AND SEX INCIDENCE OF DIFFERENT TYPES OF NON-HODGKIN'S LYMPHOMA
AFIP Otolaryngic Tumor Registry (1966-1976)

Type	Age Range (Years)	Median Age (Years)	Male	Female
Nodular lymphoma	48-72	55	3	2
Diffuse lymphosarcoma				
Prolymphocytic	7-78	64	6	6
Lymphoblastic	17-77	58	10	6
Burkitt's tumor	9-13	11	3	—
Reticulosarcoma	5-76	61	14	4

Microscopic. The non-Hodgkin's lymphomas have the microscopic appearance of collections of lymphoid cells of varying differentiation that infiltrate and replace local architecture of the tissues in which they are found.

Because of the complexity and uncertainty of the classifications of non-Hodgkin's lymphoma, the authors will not delve further into the micromorphology, but will refer the interested reader to Fascicle 8, First Series, Tumors of the Hematopoietic System by Rappaport, and the WHO's Histological and Cytological Typing of Neoplastic Diseases of Haematopoietic and Lymphoid Tissues by Mathe and Rappaport.

A general summary of the histology of non-Hodgkin's lymphoma reveals that the neoplastic infiltrate will cause effacement of the normal architecture of the anatomic area, particularly the lymphoid structures of the palatine and lingual tonsils and the nasopharynx. The anaplasia of the tumor cells may be the clue of the diagnosis of lymphoma, but in the well differentiated non-Hodgkin's lymphoma, one may have to depend on the identification of the invasion of the well differentiated lymphocytic tumor cells into surrounding fibrous capsules, striated muscles, and the walls of vessels. When involving salivary gland tissue of the upper respiratory tract, the lymphoma cells tend to infiltrate around the glandular structures without significant displacement. Invasion of overlying stratified squamous cell epithelium by the lymphoid infiltrate has been a questionable criteria pointing toward a non-Hodgkin's lymphoma diagnosis, since invasion of the mucosa of the tonsils and nasopharynx by benign underlying lymphoid cells is a normal benign occurrence. Certainly, the pathologist must make use of the recent immunologic evaluations available in questionable cases, but even with these improvements, the definite classification may require long-term clinical observation of the patient with subsequent biopsies and histologic studies (Duncavage et al.).

Differential Diagnosis. One of the most common diagnostic problems encountered by AFIP-OTR is the microscopic differentiation of non-Hodgkin's lymphoma and poorly differentiated squamous cell carcinoma. The carcinoma is particularly prone to occur in Waldeyer's ring, where lymphomas are no stranger. Certainly, immunopathologic and

electron microscopy examination has helped in making the correct diagnosis, but still it requires craftsmanship on the part of the pathologist and histotechnologist for the solution to the problem. Any small cell malignant neoplasm, such as rhabdomyosarcoma and olfactory neuroblastoma particularly, can occur in the upper respiratory tract and can also be a difficult differential problem. So-called pseudolymphomas are apparently rare in the head and neck area and, if encountered, the pathologist must be able to discriminate between the micromorphology of hyperplastic benign lymphoid proliferation and neoplastic lymphomatous cytology.

Systemic lymphocytic leukemia can infiltrate upper respiratory structures and will be indistinguishable from the micromorphology of non-Hodgkin's lymphoma. Any patient with the diagnosis of non-Hodgkin's lymphoma of the head and neck should be investigated for possible involvement by a leukemic infiltrate. Chloromas may present as a tumor in the head and neck as an initial manifestation of myelogenous sarcoma or leukemia (Brooks et al.). Infectious mononucleosis can imitate the clinical picture of non-Hodgkin's lymphoma in the head and neck even though infectious mononucleosis is more likely to occur in the younger patient. In any lymphoma diagnosis in this anatomic area, it is mandatory to perform a screening test for infectious mononucleosis.

Clinical. In primary sinonasal tract involvement by non-Hodgkin's lymphoma, the presenting symptoms listed by Kapadia and associates (1981), in order of frequency, was asymmetrical facial swelling or cheek mass, nasal obstruction, mass, or nasal discharge, with weight loss and exophthalmos being relatively rare. The lymphoma will usually be localized in the head and neck area in less than a fourth of the patients and, in the rare case, will remain so during the entire clinical course.

In patients with involvement of Waldeyer's ring area (nasopharynx, oropharynx, palatine, and lingual tonsils), the tonsil is implicated in practically half the cases, followed by the nasopharynx in a quarter, and the rest distributed in the base of the tongue, soft palate, oropharynx, and adjacent soft tissue sites. The disease will be localized to the Waldeyer's ring area in less than 15 percent of cases, with the cervical lymph nodes involved in 41.9 percent, and distant lymph nodes in 44.6 percent, when studied by lymphography (Banfi et al.). Presenting symptoms in lymphoma of the Waldeyer's ring area were local in 50 percent with nasal obstruction, earache, decreased hearing, and sore throat, and with the other half of the patients presenting with the first symptom an adenopathy in the neck and, rarely, in distal sites (Banfi et al.). When laryngeal involvement with lymphoma is diagnosed, there is a representing symptomatology of progressive difficulty in swallowing, hoarseness, and possibly dyspnea. The ear is reported to be involved by systemic lymphoma with or without signs of sudden or gradual hearing difficulty, otitis media, tinnitus, dizziness, or vertigo (Paparella and el Fiky).

Burkitt's lymphoma, the disease in the equatorial African setting, presents in the facial bones in over 75 percent of the patients, who range from 2 to 16 years, with the highest incidence between 6 and 9 years (Nkumah and Perkins). There is a 2 to 1 female to male ratio. In the United States, the primary age is between 2 to 11 years (Cohen et al.), although there is the occasional adult patient. There is a slight male predominance in this country and most patients are caucasian. The principal present-

Table 20

REVISED CLINICAL CLASSIFICATION OF HODGKIN'S DISEASE
(Amended from Peters et al.).

Stage*	Description
Stage I	Disease limited to one anatomic area
Stage II	(1) Disease limited to two contiguous anatomic regions on same side of diaphragm (2) Disease in more than two anatomic regions or in two noncontiguous regions on same side of diaphragm
Stage III	Disease on both sides of diaphragm, but limited to involvement of lymph nodes, spleen, and Waldeyer's ring
Stage IV	Involvement of tissue other than lymph nodes, spleen, or Waldeyer's ring

*Stages may be subclassified as "A" or "B" to indicate the absence or presence, respectively, of systemic symptoms.

ing symptom in the American cases was abdominal lymph node disease in 65 percent of the patients and only 20 percent had a primary jaw tumor.

Treatment and Prognosis. Radiotherapy and/or chemotherapy are unanimously the choice for therapy of the non-Hodgkin's lymphoma and the choice of either, or the combination of both, will usually depend upon the clinical situation. There has been a clinical classification of non-Hodgkin's lymphoma, such as that utilized in Hodgkin's disease (Table 20), and some treatment centers have utilized this classification in the planning of treatment.

Krueger and colleagues suggested a prognostic category arrangement according to the median year of survival with a low-grade malignant group (lymphoplasmacytic lymphoma, 6.2 years; lymphocytic lymphoma, 5.9 years; nodular mixed lymphoma, 5.2 years; and nodular histiocytic pattern, 6.1 years); intermediate-grade malignancy (lymphoblastic lymphoma, 1.5 years); and high-grade malignancy (lymphoblastic lymphoma, 1.5 years; immunoblastic lymphoma and reticulosarcoma, 1.7 years). There is no anatomic site in the upper respiratory tract that has a poorer prognosis over the other sites, unless it is the tonsil, where there is greater association with generalized disease (Evans).

HODGKIN'S DISEASE

Definition. "A malignant neoplastic disease in which typical Reed-Sternberg cells and mononuclear cells with corresponding nuclear features represent the neoplastic elements and, in which, a variety of inflammatory cells are intimately associated with the malignant cellular proliferation" (Mathe and Rappaport).

Classification and Microscopic. The micromorphologic picture of Hodgkin's disease has been consolidated into four histologic subtypes:

(1) **Hodgkin's disease with lymphocytic predominance** is characterized by an abundance of mature lymphocytes.

(2) **Hodgkin's disease with nodular sclerosis** is characterized by broad bands of collagen subdividing cellular nodules composed of Reed-Sternberg cells, lymphocytes, eosinophils, and neutrophilic mature granulocytes and plasma cells.

(3) **Hodgkin's disease with mixed cellularity.** In this form, although lymphocytes and nonneoplastic histiocytes are still the chief cellular components, Reed-Sternberg cells and mononuclear cells with corresponding nuclear features are more numerous. A wide variety of inflammatory and reactive cells (including eosinophilic and neutrophilic mature granulocytes, plasma cells, and lymphocytes) may be found. A form of lymphoma described by Lennert and Mestdagh (Lennert's lymphoma) found mainly in cases involving the palatine tonsil (Todd and Michaels) was thought originally to belong with this subtype of Hodgkin's disease. This condition is now considered to represent a distinct and highly malignant form of non-Hodgkin's lymphoma and will be discussed later.

(4) **Hodgkin's disease with lymphocytic depletion** is characterized by a paucity of lymphocytes. The histologic form of the disease shows some relation to survival with lymphocyte predominance representing the highest survival and lymphocyte depletion the lowest.

Incidence. There were 10 patients with nasopharyngeal Hodgkin's disease recorded in the AFIP-OTR, 4 of whom had oropharyngeal and hypopharyngeal Hodgkin's disease. Of the 38 tumors in the nasopharynx and pharynx recorded in the world literature, 15 were known to be in males and 22 in females. The age at the time of initial diagnosis varied from 7 to 70 years, with a peak of 9 patients in the fifth decade of life. Only 10 patients were found to be free of tumor elsewhere in the body at the time of diagnosis and can thus be considered to have had primary nasopharyngeal Hodgkin's disease (Todd and Michaels). It is possible that Hodgkin's disease may involve the nasopharynx more frequently in an occult form in the course of the disease process (Biorklund et al.).

The tonsil is a more common site of Hodgkin's disease in the upper respiratory tract, with 30 cases recorded in that organ and 4 cases noted involving the larynx during a 30-year survey of the AFIP-OTR.

Clinical, Treatment, and Prognosis. Table 20 presents the clinical classification of Hodgkin's disease adapted from Peters and associates. Appropriate management of Hodgkin's disease is based on both the clinical stage of the disease and the specific anatomic sites of involvement within each stage, while the histopathologic subclassification has become less important (Fuller and Hagemeister). Their five-year survival figure for clinically staged I and II patients is 95 percent. The corresponding result for stages IIIA and IIIB is 85 percent and a 67 percent five-year survival for stage IV patients. Therapy will vary in different institutions; however, irradiation with or without combination chemotherapy in the advanced clinical stages has been the general rule. Patchefsky and associates, in a retrospective clinicopathologic analysis of 235 cases, noted that the lymphocytic depletion group was evenly distributed over all stages; nodular sclerosis cases most commonly presented in stages I and II, while mixed cellularity and lymphocytic predominant groups were evenly distributed. They felt patients with nodular sclerosis had a favorable prognosis only in stages I and II, while patients with mixed cellularity and lymphocytic depletion had an unfavorable prognosis regardless of clinical stages. Poor survival was associated with a

late stage, male sex, older age, and systemic symptoms.

Malignant Lymphoma with a High Content of Epithelioid Histiocytes (Lennert's Lymphoma). This disease is felt to represent a non-Hodgkin's lymphoma in which there are clusters of cells of granulomatous appearance forming discrete groups, but separated and sometimes interspersed with normal lymphocytes (figs. 229, 230). Epithelioid histiocytic cells with abundant pale-staining cytoplasm comprise the majority of the cellular infiltrate. Reed-Sternberg-like cells are infrequent, but there are also giant cells of the Langhans type. Eosinophils may be prominent. The entity, most commonly seen in middle aged or elderly patients (fifth and sixth decades), is characterized by lymphadenopathy (especially cervical) and variable involvement of Waldeyer's ring, bone marrow, liver, and spleen. An allergic history and polyclonal hyperglobulinemia are common. The clinical course and response to therapy are unpredictable; death has frequently resulted from sepsis or diffuse lymphomatous involvement (Holinger et al.).

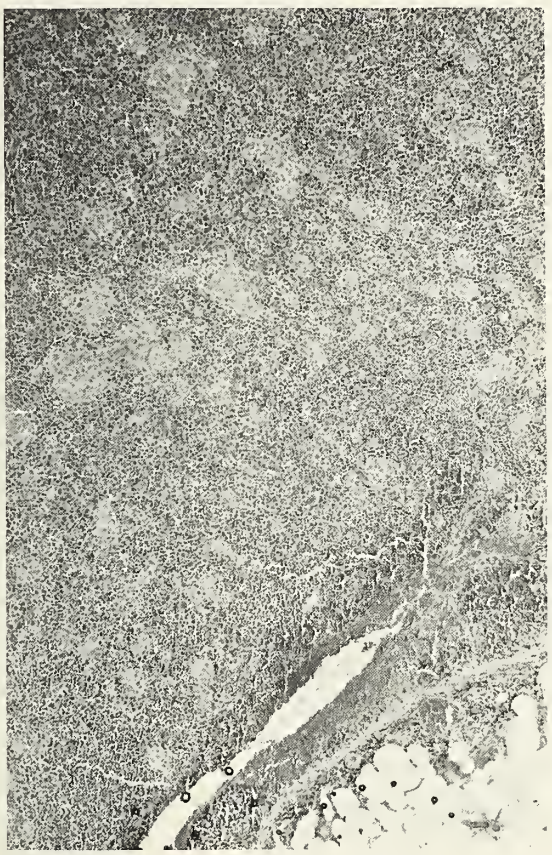

Figure 229
(Figures 229 and 230 are from the same patient)
LENNERT'S LYMPHOMA
A Lennert's lymphoma of the tonsil with distinct granulomatous areas interspersed among lymphocytes. X63.

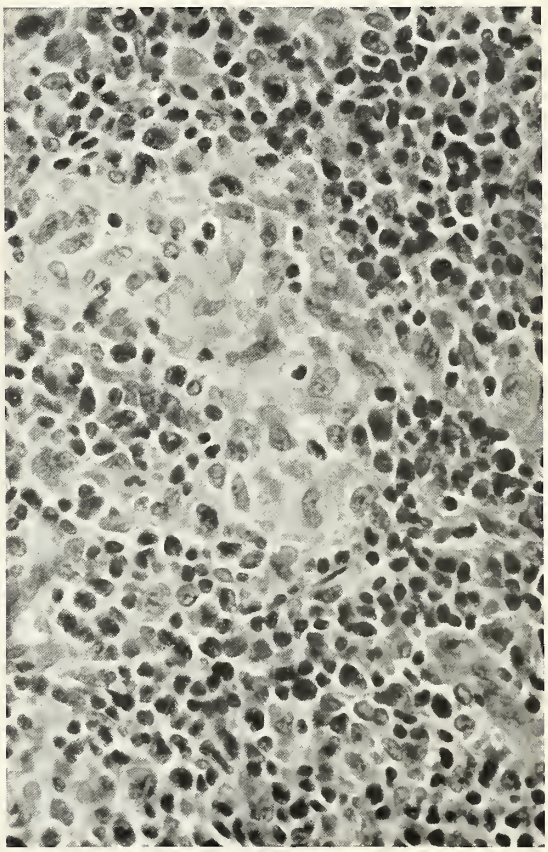

Figure 230
LENNERT'S LYMPHOMA
Higher magnification of figure 229 reveals the epithelioid type histiocytic cell collection amidst the lymphocytes. X400.

Burke and Butler and Kim and associates managed the disease in the early clinical stages with radiation and the more advanced cases by chemotherapy alone or in combination with radiotherapy. The response to treatment is poor, with only a quarter of patients showing a satisfactory response, and then usually for only a short interval. In the four patients of Holinger and associates involving the head and neck region, three were dead by 14 months, while one was alive at five years.

Natural History of Lymphoma of the Upper Respiratory Tract. Many patients with lymphoma elsewhere in the body are observed to develop lymphomatous changes in the upper respiratory tract as the course of the disease progresses. A considerable proportion of lymphomas commence in the upper respiratory tract before spreading to other parts. More than half of all cases of reticulosarcoma and one-fifth of all lymphosarcomas presented primarily in the upper respiratory tract in the large study of Banfi and colleagues. At the time of presentation, cervical lymph node extension was common in their patients. As many as 44.6 percent of upper respiratory tract patients showed extension of the lymphomatous process to retroperitoneal and inguinal lymph nodes by lymphangiography. Involvement of the gastrointestinal tract, particularly the stomach, either at the time of admission or early in the followup, was 20 percent in that series.

There appears to be a high survival rate in cases of reticulosarcoma of the pharynx when there is no involvement of the cervical nodes (7 out of 9 patients in this clinical situation survived five years or more). On the other hand, almost all the patients with involvement of the cervical nodes by reticulosarcoma had early recurrences or metastases that failed to respond to various therapeutic measures (Al-Saleem et al.). In that study, lymphosarcoma of the pharynx showed more tendency to disseminate, but recurrences were relatively easier to control by radiotherapy or chemotherapy and were compatible with long survival. Nodular lymphosarcoma has a better outlook than the other lymphomatous processes.

MIDLINE MALIGNANT RETICULOSIS (LETHAL MIDLINE GRANULOMA)

SYNONYMS AND RELATED TERMS: Stewart's granuloma; non-healing granuloma; polymorphic reticulosis; granuloma gangrenescene; necrosis with atypical cell exudate.

Definition. Midline malignant reticulosis is a rare, progressive, destructive lesion, usually involving initially the midpalate and/or the nasal septum and, if not responsive to therapy, may involve the facial area with a hideously appearing ulcerative lesion. Histologically, the picture is that of a mixed atypical lymphoreticular infiltrate accompanied by varying amounts of necrosis.

This presentation presumes that this pathologic entity is a form of lymphoma (? histiocytic non-Hodgkin's lymphoma). There has been speculation whether or not this process represents a localized Wegener's granulomatosis (Friedmann); however, the experience gained from AFIP-OTR does not support this assumption clinically or histologically. Also, there is a designation of "idiopathic midline destructive disease" (Tsokos et al.) that is considered a locally destructive lesion responsive to radiotherapy, but which supposedly consists of only acute and chronic inflammation without presence of malignant or atypical cells. The AFIP-OTR material does not contain such an entity. Perhaps this discrepancy is due to individual microscopic interpretations of the inflammatory cell infiltrate.

There is the question as to whether this midline malignant reticulosis represents a sinonasal and palatine form of lymphomatoid granulomatosis of Liebow and associates. This is certainly possible (DeRemee et al.), but the disease processes described by Liebow and colleagues were not similar to the clinical involvement of the midline malignant reticulosis and some may argue whether it is similar histologically (Aozasa).

Clinical. Patients ranged in age from 11 to 88 years, with an average of 48 years. Published series reveal a definite male predominance varying from a 4 to 1 to 9 to 1 male to female ratio. Patients are mostly caucasian with no blacks reported. Latins, orientals, and those of Arabic descent have been included in case reports.

The symptoms primarily are those of unilateral nasal obstruction (Michaels and Gregory), often for many years. Otitis media is not an unusual presenting symptom. Most patients have an accompanying unilateral or bilateral maxillary sinusitis. Patients, early in the disease, have shown no particular constitutional symptoms other than the local findings in the upper respiratory tract and oral facial region. Nasal obstruction or inflammatory symptoms eventually give way to ulceration and destruction of parts of the nasal cavity with varying degrees of involvement of the nasal septum, turbinate bones, ethmoid sinuses, hard palate, and lateral wall of the nose (figs. 231, 232). There may be an extension of the process into the nasopharynx, orbit, or the base of the skull. Death is related to either infection or massive hemorrhage.

Microscopic. A histologic change of a rather specific type can be correlated with the malignant activity ascribed to this condition (Michaels and Gregory) (figs. 233, 234). There is widespread necrosis, together with some areas of atypical cellular exudate. The atypical cells are somewhat larger than inflammatory cells, with nuclei that vary from

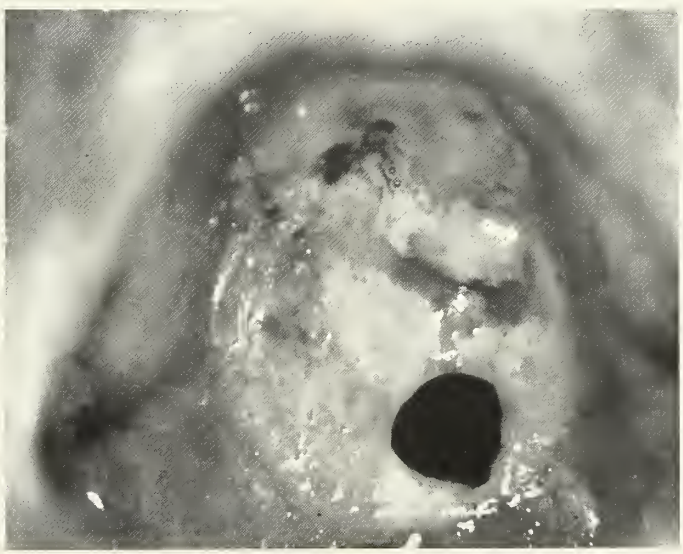

Figure 231
MIDLINE MALIGNANT RETICULOSIS
The clinical presentation of a progressive midline destructive palatal and nasal septal process in a 45 year old man was felt, clinically and histologically, to represent midline malignant reticulosis.

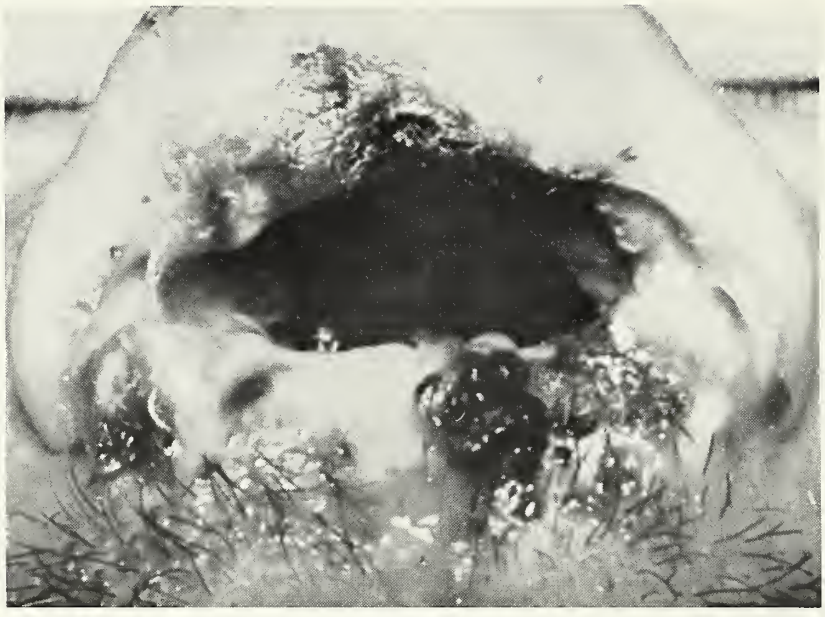

Figure 232
MIDLINE MALIGNANT RETICULOSIS
In this midline malignant reticulosis in a 40 year old man, the entire nasal septum and bilateral nasal walls were destroyed.

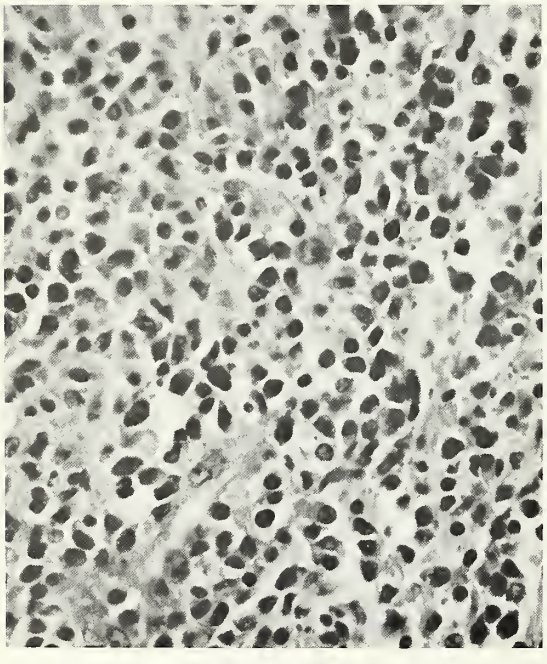

Figure 233
MIDLINE MALIGNANT RETICULOSIS
Note atypical mixed cellular infiltrate representing the cytology of a lymphomatous infiltrate. X400.

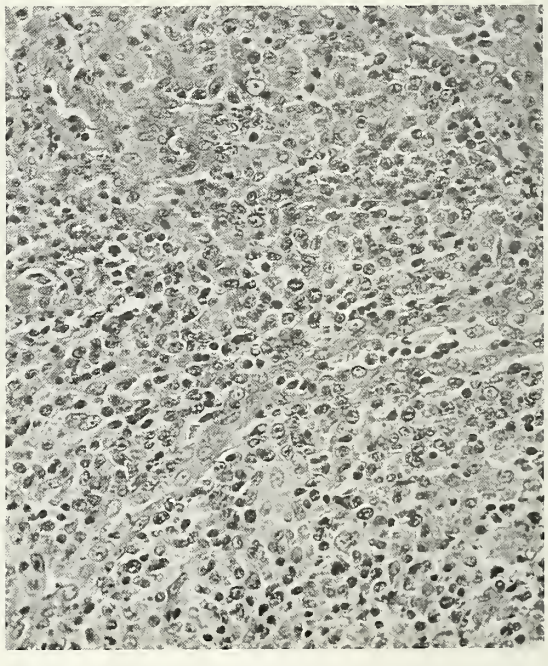

Figure 234
MIDLINE MALIGNANT RETICULOSIS
This histology from a case of midline malignant reticulosis is that of histiocytic lymphoma-like infiltrate. X250.

round to horseshoe-shaped and have irregular protuberances. Chromatin material is irregularly distributed. Binucleate forms are present and mitotic figures are seen among the atypical cells. The cytoplasmic membrane is indefinite. Phagocytized basophilic debris is frequently seen in the cytoplasm of the cells. Zones composed of such cells vary from very small areas to large parts of the available biopsy material. Necrosis is always prominent and is usually of the coagulative type. It is present between the tumor cells and also forms large eosinophilic cellular areas that frequently form a prominent feature of the biopsy material. The atypical cells possess a fine reticulin pattern which surrounds each cell. Large areas of the necrotic zones show a similar reticulin framework. The atypical cell infiltrate may be seen invading nerve, skeletal muscle, or bone. A frequent finding is the invasion of the arterial walls by the atypical cells which can be mistaken histologically for a primary arteritis (fig. 235).

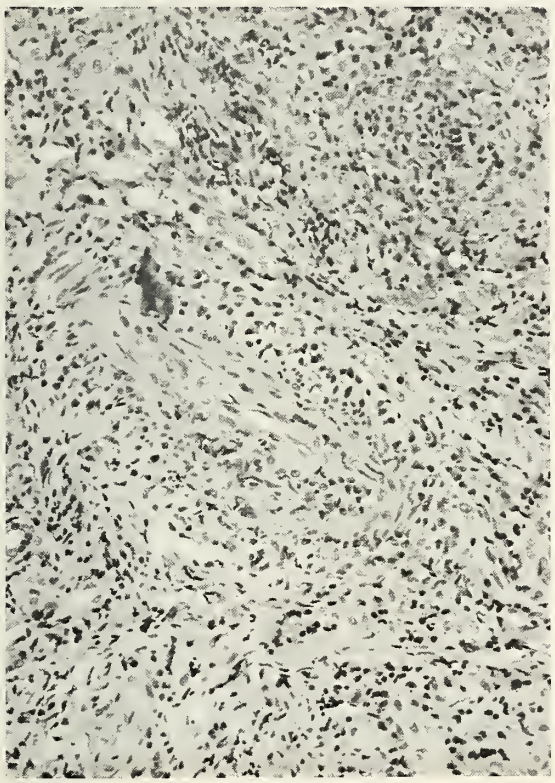

Figure 235
MIDLINE MALIGNANT RETICULOSIS
A vessel with infiltration of the atypical lymphocytes into the wall. X63.

At first biopsy, histologic findings were more frequently polymorphic and less frequently monomorphic. As the disease progressed, the monomorphic nature of the neoplastic infiltrate usually became more obvious. Survival could not be predicted from biopsy findings. Surface markers and enzyme cytochemical studies support the atypical cells as histiocytic in nature (Aozasa).

Differential Diagnosis. Table 21 reveals a graphic illustration of the problem accompanying the so-called hole in the head differential diagnostic problem. Sixty-nine patients in the AFIP-OTR material presented destructive ulcerative lesions of the sinonasopalatine area conforming, at least originally, to the clinical entity of "lethal midline granuloma." Follow-up information on these 69

Table 21

SUBSEQUENT ETIOLOGIC DISEASE ENTITY ESTABLISHED IN 69 CASES WITH INITIAL CLINICAL AND HISTOLOGIC DIAGNOSIS OF "LETHAL MIDLINE GRANULOMA"
AFIP Otolaryngic Tumor Registry

	No. Cases
Process healed satisfactorily without specific therapy	12
Squamous cell carcinoma	6
Tuberculosis	5
Syphilis	4
Wegener's granulomatosis	13
Miscellaneous disease entities (neoplastic, infectious, idiopathic)	20
"Lethal midline granuloma"	9

lesions revealed that only 9 were eventually felt to be midline malignant reticulosis.

Wegener's granulomatosis was the most common entity causing differential diagnostic confusion. The patients with Wegener's granulomatosis usually had systemic symptoms plus the histologic appearance was that of a type of focal necrosis surrounded by acute and chronic inflammatory reaction, often including multinucleated reactive giant cells. A primary arteritis must be searched for. The specific therapeutic regime demanded in Wegener's granulomatosis necessitates an extensive effort to confirm the diagnosis.

The occasional small biopsy specimen will be a problem, especially by causing a neoplastic histology to be overlooked. Among the neoplastic diseases also causing confusion is "histiocytosis X." Snyder and associates reported nine cases of nasal septal perforation in systemic lupus erythematosus. The AFIP-OTR experience also enforces the possibility of nasal septal perforation secondary to cocaine "sniffing." In this situation, only nonspecific granulation tissue is seen histologically, but occasionally starch granules used as a cocaine dilutant are noted within the tissues.

Treatment and Prognosis. Radiotherapy in a lymphoma dose schedule appears the most preferred and effective treatment. Chemotherapy alone has not been efficacious. Of the 10 patients reported by Michaels and Gregory as having midline malignant reticulosis, 4 died within six months to five years; however, the remaining 6 patients were alive and well nine months to three years, all treated with radiotherapy. Fechner and Lamppin, in a literature search, quoted survival of up to five years following radiation therapy. Eichel and associates reported a 100 percent survival in 9 patients following radiation therapy. Fu and Perzin reported 3 patients with midline malignant reticulosis treated with radiotherapy who died at three, seven, and eight months following diagnosis. Aozasa studied 19 patients having a range of survival from 4 to 40 months (mean 13.8 months), with 90 percent of the patients dying before two years. Additional support for the midline malignant reticulosis being a lymphoma is the later dissemination of the disease. Fechner and Lamppin, in evaluating 21 patients including 3 of their own, considered 11 to have disseminated disease. Michaels and Gregory described regional and distal lymph nodes involved with lymphoma in 4 of their 10 patients.

EXTRAMEDULLARY PLASMACYTOMA

SYNONYMS AND RELATED TERMS: Solitary extramedullary plasmacytoma; soft tissue extramedullary plasmacytoma.

Definition. For the purposes of this presentation, extramedullary plasmacytoma is defined as a circumscribed mass or infiltrate in the soft tissue, composed almost entirely of what is felt to be atypical and presumably neoplastic plasma cells. This infiltrate must be distinguished from a reactive plasma cell condition and a local manifestation of systemic plasma cell disease, such as multiple myeloma. Recent studies (Wiltshaw) indicate that extramedullary plasmacytoma may constitute a different entity from both solitary plasmacytoma of bone and multiple myeloma, based on its different mode of spread and higher survival rate as well as the type of its presentation; however, a varying percentage of extramedullary plasmacytoma in literature may be associated, particularly at a later time, with multiple myeloma or solitary osseous myeloma.

Incidence. An incidence of 41 males and 12 females in the 53 AFIP-OTR patients has a similar male preponderance as that of the

series of Kapadia and associates (1982), Stout and Kenney, Castro and associates, and Wiltshaw. The age incidence of the AFIP-OTR patients was from childhood to the elderly, but centered in the 40 to 80 year age group, similar to other published series.

Sites of Presentation. Soft tissue extramedullary plasmacytomas present in the mucosa or submucosa of the upper respiratory tract. Table 22 lists the site of presentation in the AFIP-OTR series. Nasal septum and lateral wall of the nose were equally prone to the development of this lesion and the invasion of paranasal sinuses, particularly the maxillary antrum, was common.

Gross. In 20 percent of the AFIP-OTR patients, the tumor was polypoid, otherwise it presented usually as a mucosal covered gray to red, soft, or rubbery mass.

Microscopic. The large sheets of monotonous cells replacing tissue structures and invading locally are the hallmarks of the neoplasm (figs. 236-238). Blood vessels are usually the only other structures seen within the tumor, although occasionally the cells appear to be adherent to or supported by the vessels. There is an occasional resemblance to an alveolar pattern, with an eosinophilic exudate within a central space that suggests a gland. The neoplastic cell may be indistinguishable from the normal plasma cell with the eccentrically situated nucleus containing five to eight deeply basophilic masses of chromatin arranged in the so-called cartwheel fashion. The cytoplasm is nongranular and basophilic with, occasionally, a lightly stained area (the paranuclear "vacuole") near the nucleus. Rarely, Russell bodies (50 to 150 micron spheroidal, homogenous, eosinophilic, cytoplasmic bodies) are seen. They were noted in 7 of the 53 cases contained in the AFIP-OTR. However, they are most often seen in the reactive plasma cell infiltrate. In properly prepared material, there may be varying amounts of less differentiated cells which lose the "cartwheel" pattern of the nucleus along with an increase in nuclear size. Mitotic figures are seen only in the neoplasm, not in plasma cell reactive granulation tissue. Marked nuclear anaplasia, giant nuclei, and numerous mitotic figures may be correlated with a more aggressive behavior. The nuclear diameters of at least 100 tumor cells in each of 14 cases of plasmacytomas of the upper respiratory were determined. After at least one year post measurement, those cases that revealed local or distant metastasis had mean nuclear diameters greater than 6 microns, while those lesions with mean diameters less than 6 microns acted in a benign fashion. We have not found the presence of binucleated or multinucleated forms, common in all grades of plasmacytoma, to be of any value in assessing the behavior of these lesions. In the more undifferentiated neoplasm, the plasma cell origin becomes more difficult to recognize and distinction from such tumors as

Table 22

SITES OF INITIAL PRESENTATION IN 53 CASES OF SOFT TISSUE EXTRAMEDULLARY PLASMACYTOMA OF THE UPPER RESPIRATORY TRACT
AFIP Otolaryngic Tumor Registry (1940-80)

	No. Cases
Sinonasal cavity area	28
Nasopharynx	10
Pharynx (oro and hyopharynx included)	3
Tonsil	3
Larynx	
Ventricular fold	3
True vocal cord	1
Supraglottis	3
Epiglottis	2

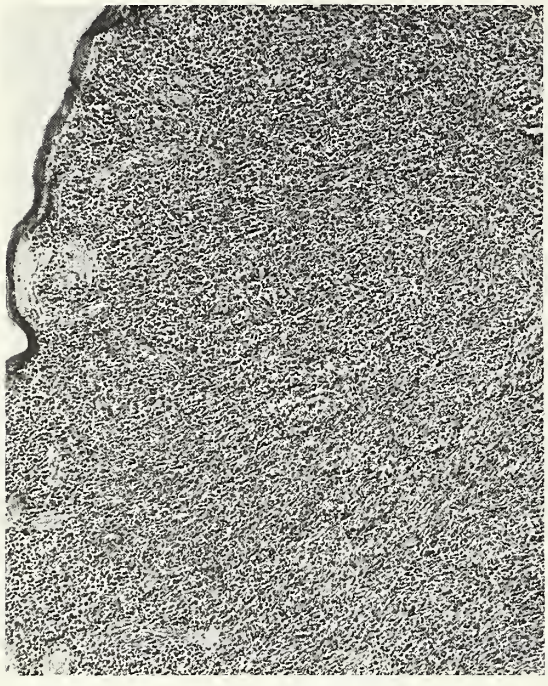

Figure 236
(Figures 236 and 237 are from the same patient)
EXTRAMEDULLARY PLASMACYTOMA
In this soft tissue extramedullary plasmacytoma of the nasal cavity, the monotony of the cell infiltrate is obvious. X63.

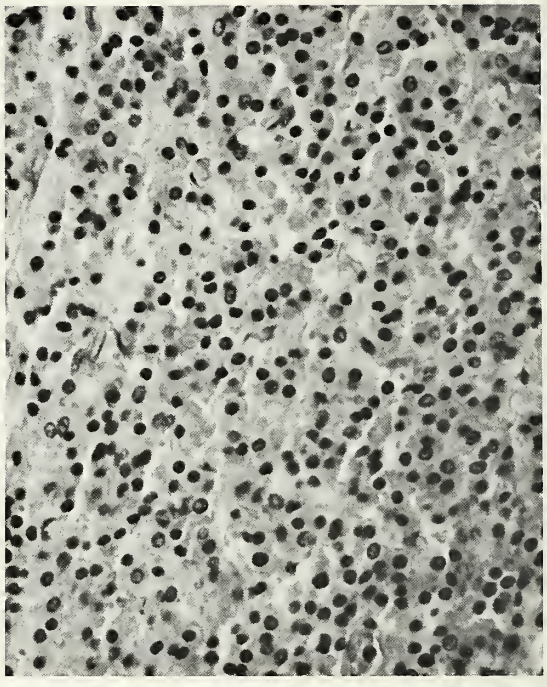

Figure 237
EXTRAMEDULLARY PLASMACYTOMA
Note the monotony of the well differentiated plasma cells, with no evidence of other cells. X400.

undifferentiated carcinoma, amelanotic melanoma, or reticulosarcoma may be quite difficult.

In multiple myeloma of the skeletal system, about 10 percent show deposits of amyloid (Lichtenstein and Jaffe). Amyloid deposits are seen even more frequently in plasmacytoma of the upper respiratory tract. In a series of 53 cases of plasmacytoma of the upper respiratory tract contained in the AFIP-OTR material, 20 percent revealed large deposits of amyloid involving at least one-third of the tumor tissue. These plasmacytomas with prominent amyloid were located in the ventricular fold of the larynx, the nasal cavity, and Waldeyer's ring. The presence of amyloid with the extramedullary plasmacytoma of the head and neck had no apparent prognostic significance, since it occurred in both well differentiated local tumors as well as more aggressive undifferentiated plasmacytomas. The metastatic focus from these did not contain amyloid. Of interest is the observation that Russell bodies and amyloid have not been found in the same neoplasm.

One important observation in the distinction of the soft part extramedullary plasmacytoma from the reactive plasma cell granuloma is the absence of any other inflammatory cells or mixture thereof in the nonnecrotic area of the former.

Immunoglobulin Levels. In none of the AFIP-OTR patients, and very rarely in the literature, has elevation of serum immunoglobulin or the presence of urinary Bence Jones protein been detected in the presentation of the neoplasm. In Wiltshaw's Royal Marsden series, about 10 percent of all

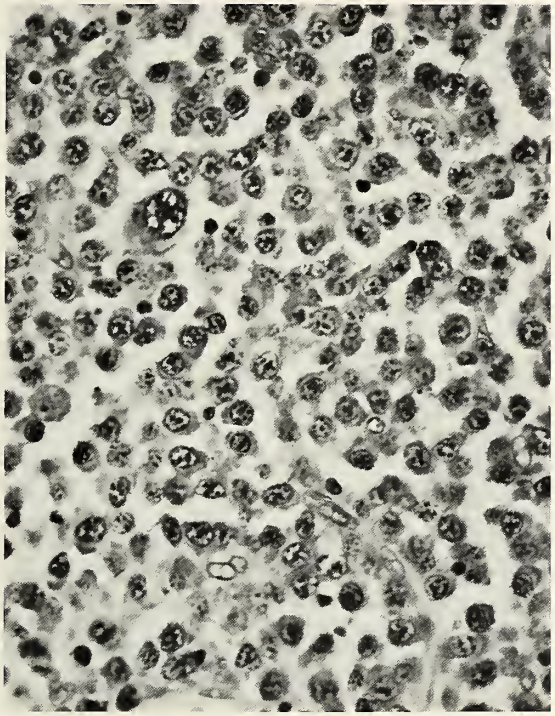

Figure 238
EXTRAMEDULLARY PLASMACYTOMA
A soft tissue extramedullary plasmacytoma of the head and neck area reveals more anaplastic cytology of the neoplastic cells, which may, on occasion, make the recognition of a plasma cell genesis difficult. X400.

patients, who were usually in the advanced stage of the disease with large amounts of tumor mass, subsequently developed paraproteinemia.

The use of the immunoperoxidase staining method on paraffin embedded formalin fixed sections of plasmacytomas has shown that, like multiple myeloma, these tumors secrete immunoglobulin in a monoclonal fashion. The heavy chain produced is always IgG and the light chains may be either kappa or lambda. The determination of monoclonal immunoglobulin is a useful aid in determining whether a particular collection of plasma cells is a plasmacytoma and also in identifying an undiagnosed tumor as a plasmacytoma.

Clinical. Manifestations, in order of decreasing frequency, were a soft tissue mass, airway obstruction, epistaxis followed by tumor associated pain, nasal discharge, and regional lymphadenopathy. Proptosis occurred with orbital involvement, but cranial nerve involvement was rare (Kapadia et al., 1982). Woodruff and associates clinically staged soft tissue extramedullary plasmacytoma as stage I — tumor confined to the primary site; stage II — involvement of draining lymph nodes; and stage III — evidence of metastatic spread. Fourteen of 16 patients they discussed were stage I. Chronic infection, particularly sinusitis, was a prominent symptom of 5 of 10 patients with extramedullary plasmacytoma of the head and neck presented by Bush and associates. With laryngeal involvement, besides obstruction of the airway, vocal cord paralysis may be a part of the clinical presentation. There was no case of primary plasmacytoma involvement of the temporal bone in the AFIP-OTR data.

Treatment, Natural History, and Prognosis. The literature uniformly favored radiotherapy with the occasional surgical removal of a polypoid tumor. Harwood and associates favored a total dose of 3500 rads in 15 fractions over a three week period. In their series of 23 patients, 14 were alive with no evidence of disease from 7 months to 14 years (average 8 years). One patient was alive three years with disease. Four patients died with multiple myeloma. Three died of unrecognized or other causes. One died with regional and distal extramedullary myeloma. Medini and colleagues reported 7 patients with upper respiratory tract soft tissue extramedullary plasmacytoma treated with radiotherapy and all are alive with no evidence of disease 3 years to 24 years (median 12 years). In the large series of extramedullary plasmacytoma

of Wiltshaw, 19 percent developed single deposits in bone. In 18 percent, there was lymph node spread, but in one third of these cases, the lesion developed no further than the draining lymph nodes. There was a 50 percent survival rate of 10 years or better. Fu and Perzin summarized the outlook in soft tissue extramedullary plasmacytoma of the upper respiratory tract. They stated that some patients have localized disease, which is apparently controlled by surgery, radiotherapy, or both, and which never recurs locally or becomes disseminated. Other patients have recurrence locally and are controlled by further therapy. Other patients have a locally persistent and aggressive lesion which cannot be eradicated and which eventually leads to the patient's death by uncontrolled local growth. Finally, some patients eventually develop evidence of plasma cell neoplasms elsewhere in the body and/or multiple myeloma.

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NEUROECTODERMAL LESIONS

A growing body of evidence continues to accumulate which implicates the neural crest and/or neuroendocrine type cells in the derivation of a variety of tumors in diverse sites. A considerable display of these tumors is manifest in the upper airway. These lesions, and others derived from the neuroectoderm, take the form of congenital or acquired processes, hamartomatous developments, and true neoplasms. They are: granular cell tumor; heterotopic glial tissue; the derivative of the Schwann cell (neurilemoma, neurofibroma, neurogenous sarcoma, and traumatic neuroma); paraganglioma; meningioma; lesions in the upper aerodigestive tract from the pharyngeal and intracranial hypophysis; malignant melanoma; olfactory neuroblastoma; and other tumors of putative neuroendocrine origins.

GRANULAR CELL TUMOR

SYNONYMS AND RELATED TERMS: Granular cell myoblastoma; Abrikossoff's tumor; granular cell schwannoma; lipoid thesaurismosis; granular neurofibroma.

Definition. A controversial lesion, the granular cell tumor occupies an ill-defined position between reactive hyperplasia and a benign neoplasm. Since its first description in 1926, over 1200 cases have been reported in the literature. This lesion is characterized by large cells having finely granular eosinophilic cytoplasm.

Histogenesis. Controversy exists over the cell of origin of the granular cell tumor (Sobel and Marquet; Frable and Fischer). Originally it was thought that it arose from myoblasts in response to local trauma or inflammation, hence, its earlier name — granular cell myoblastoma. Other theories include genesis from histiocytes, fibroblasts, and neuroectodermal derivatives, i.e., the Schwann cell. Very likely, no single cell type is responsible for all the forms of granular cell tumors and perhaps various sheath cells with histiocyte-like potential are the cells of origin. Therefore, granular cell sheath lesion has been proposed (Eversole). In light of the controversy, WHO has proposed the noncommittal name of granular cell tumor. Despite the popularity of the perineural fibroblast theory of genesis, it is difficult to ascribe a neural origin to all granular cell tumors. Thus, the development of granular cell tumors in the cervices of newborn mice after estrogenic stimulation would suggest a myogenic origin in some instances. The growth of a tracheal granular cell tumor during pregnancy has similar implications. Sobel and Marquet's studies indicate the granular cell tumor is derived from an undifferentiated mesenchymal (fibroblast-like) cell. They present light and electron microscopic criteria to distinguish the granular cell lesions.

Sites of Tumor. The tumor has been recorded in virtually every organ and tissue of the human body (Table 23) (Peterson). Approximately one-third to one-half of all the tumors occur in the tongue and about a third appear in the skin.

Granular cell tumor presents in essentially two forms in the upper aerodigestive tract: those occurring on the gum pads in the newborn (congenital epulis) and those occurring in later life beneath the mucous membrane of the upper aerodigestive tract.

Table 23

BENIGN GRANULAR CELL TUMOR SITES*

Location		No.	Percentage
Subcutaneum		123	32.6%
Oral cavity		107	28.1
Tongue	87		23.0
Lip	10		2.6
Buccal mucosa	6		1.5
Floor of mouth	2		0.5
Palate	2		0.5
Breast		60	15.9
Larynx		29	7.6
G.I. Tract		16	4.7
Bronchus		13	3.4
Perineum		9	2.4
Hypophysis		9	2.4
Miscellaneous		11	2.9
Total		377	100.0

*After Peterson

Congenital Epulis

Because of its position and the early age of the patients, congenital epulis is considered a separate diagnostic entity. The congenital epulis is microscopically similar, if not identical, to the other forms of granular cell tumor. It has an 8 to 1 predominance in females and occurs three times more often in the maxilla than in the mandible, although both can be involved simultaneously. It is located on the crest of the alveolar ridge in the incisor region.

Objective histologic differences between the epulis form of granular cell tumor and others are: (1) a relatively high degree of vascularity not present in other granular cell tumors; (2) a lack of overlying pseudoepitheliomatous hyperplasia; and (3) a lesser degree of differentiation ultrastructurally.

The lack of pseudoepitheliomatous hyperplasia might be explained on the basis of a more rapid proliferation so that pressure results in a thinning rather than a hyperplasia of the covering epithelium.

The congenital epulis is a benign lesion, does not recur, and has been reported to regress spontaneously.

MUCOSAL GRANULAR CELL TUMORS

Incidence. The nonepulis form of the tumor is a lesion of young adult life. The median age of those presenting in the larynx is 36 years, with the majority of tumors occurring between the ages of 29 and 42 years. There is a slight female predominance.

Gross. In the upper respiratory tract, most granular cell tumors have been solitary nodules ranging from 0.3 cm to 3.0 cm in diameter. They are sessile or polypoid and rarely manifest an ulcerated surface (fig. 239).

Microscopic. The cells are distended in appearance and arranged in strands, cords, or clumps. The round to polyhedral and pale acidophilic cells manifest a marked cytoplasmic granularity (figs. 240, 241). The granules are mixed, most being small and fuzzy and a few large and well defined. The nuclei are usually small and vesicular or densely hyperchromatic (fig. 242). They are centrally located and only rarely manifest mitoses. The lesion is unencapsulated and poorly circumscribed, conveying an impression of infiltrative growth.

The granules of the cells vary in size, usually being minute, but on occasion being as large as an erythrocyte. The granules are PAS positive (variable intensity) and consistently diastase resistant. The granules stain with Alcian blue at pH 2.5. With trichrome stains, the granules are uniformly red or maroon. Periodic acid-silver methenamine reacts positively with the larger granules.

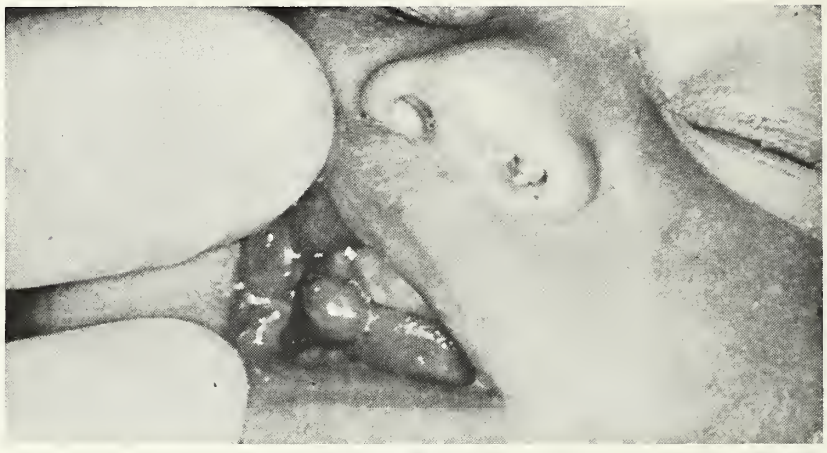

Figure 239
GRANULAR CELL TUMOR
This small mass, which presented on the alveolar ridge in the incisor area, was histologically confirmed as a granular cell tumor (congenital epulis).

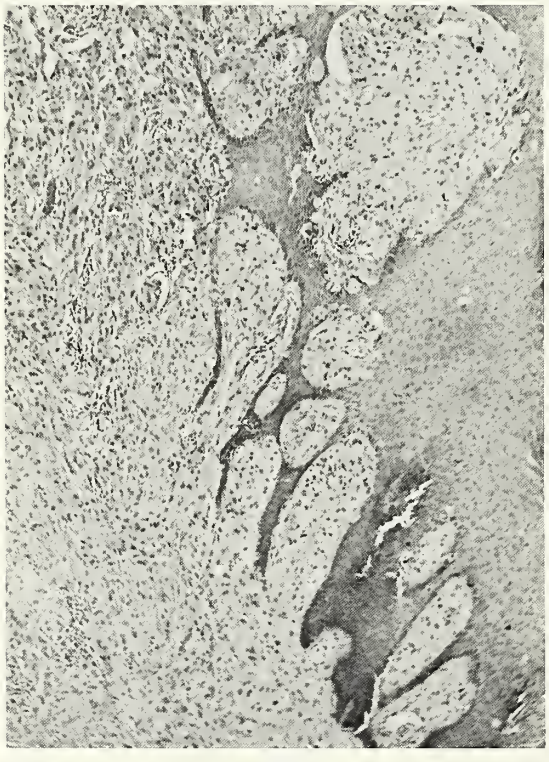

Figure 240
(Figures 240 and 241 are from the same patient)
GRANULAR CELL TUMOR
A granular cell tumor of the external auricle (pinna) shows prominent pseudoepitheliomatous hyperplasia of the overlying epidermis. X63.

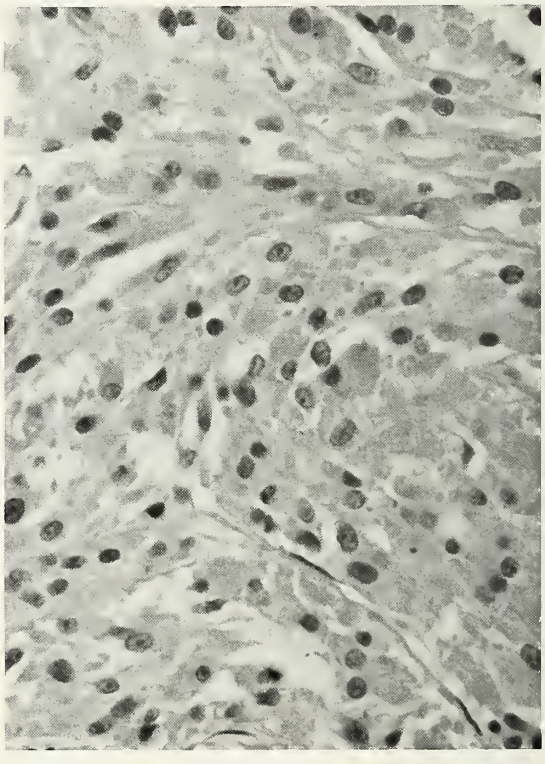

Figure 241
GRANULAR CELL TUMOR
Note the fascicular arrangement of the tumors cells, which are round to polyhedral with pale acidophilic cytoplasm manifesting a marked granularity. X400.

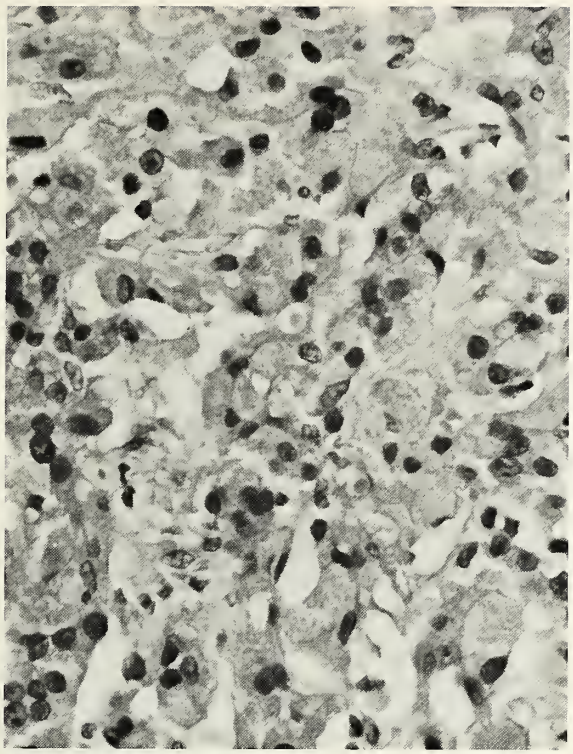

Figure 242
GRANULAR CELL TUMOR
This laryngeal granular cell tumor shows the characteristic small, round, red, cell-like bodies surrounded by a clear space. The nuclei are small and vesicular to round with a dense hyperchromasia. X400.

Acid phosphatase reactivity is similar. The granules are variably sudan-positive.

On occasion, cells with large, strongly PAS-stained, "needle" shaped bodies (angulate bodies, pustular bodies of Milan) may be seen with the light microscope. The cells containing these bodies are usually found in collagenous tissue near fascicles of myoblastoma; often they are near vascular channels. Ultrastructural findings indicate granular cells represent an unusual degenerative process (figs. 243, 244) characterized by autophagic-type vacuolar change (Regezi et al.).

Unlike the congenital epulis, pseudoepitheliomatous hyperplasia of the overlying mucosa in the upper respiratory tract granular cell tumors is common, ranging from 50 to 64 percent of cases (fig. 245). In their study of laryngeal granular cell tumors, Compagno and associates found that this feature was a significant diagnostic problem in only 22 percent of their cases. The overlying squamous epithelium rarely, if ever, will be the site of a squamous cell carcinoma.

Sites of Mucosal Tumors. In the upper respiratory system, granular cell tumors occur most frequently in the larynx (Compagno et al.). The most common location is on the posterior true cord, but they may occur in the subglottic and supraglottic areas. The next most common site of occurrence in the respiratory tract is the bronchus (Canalis et al.). The trachea is the least common area involved in the upper airway.

Natural History. Granular cell tumors, reactive or true neoplasms, are essentially benign. In those lesions lacking an apparent circumscription, the microscopic extension cannot be appreciated at the time of surgery

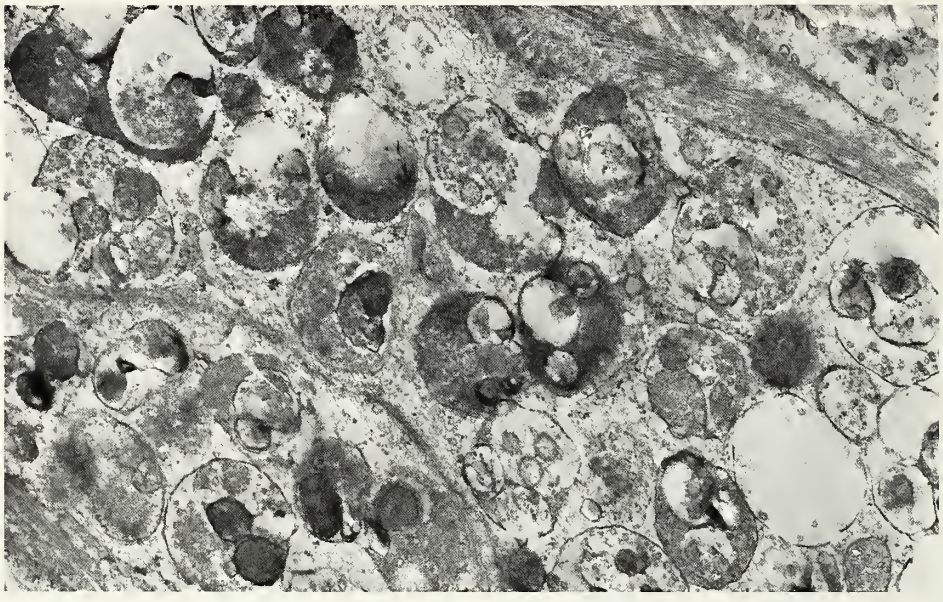

Figure 243
GRANULAR CELL TUMOR
Ultrastructural study of a granular cell tumor shows large polyhedral cells containing abundant cytoplasmic autophagic-type granules and various sized vesicular bodies. Uranyl acetate and lead citrate. X15,000. (Fig. 4 from Regezi, J.A., Batsakis, J.G., and Courtney, R.M. Granular cell tumors of the head and neck. J. Oral Surg. 37:402-406, 1979.)

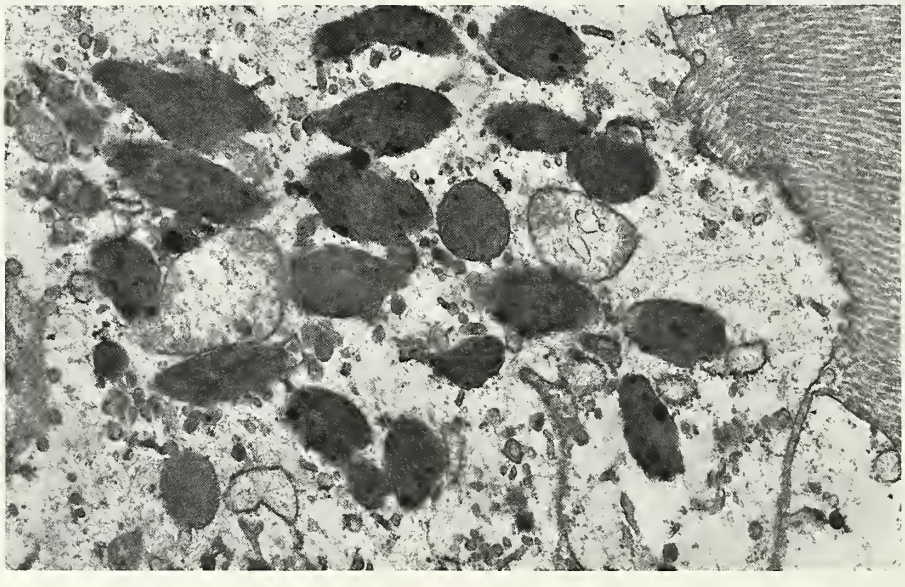

Figure 244
GRANULAR CELL TUMOR
An electron micrograph of the cytoplasm of a granular cell that contains numerous angulate bodies. Uranyl acetate and lead citrate. X15,000. (Fig. 7 from Regezi, J.A., Batsakis, J.G., and Courtney, R.M. Granular cell tumors of the head and neck. J. Oral Surg. 37:402-406, 1979.)

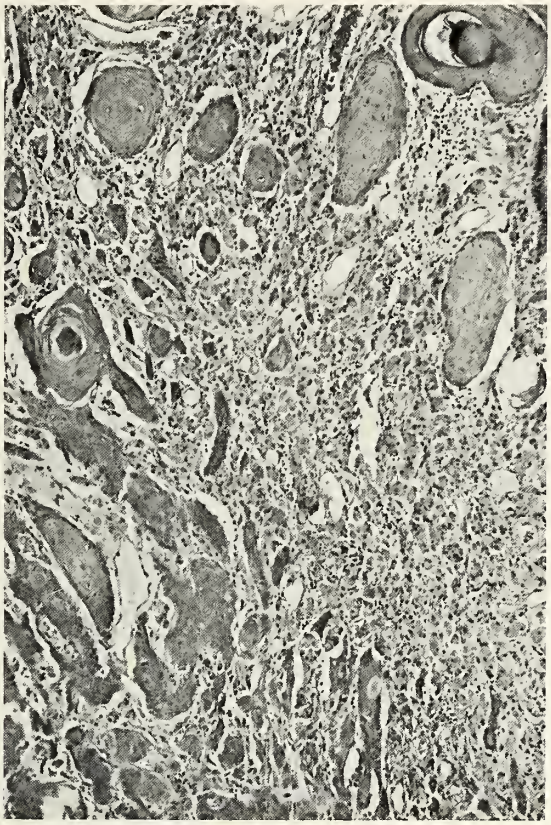

Figure 245
GRANULAR CELL TUMOR
A microscopic section of a head and neck granular cell tumor with marked pseudoepitheliomatous hyperplasia of the overlying epidermis. The often mistaken diagnosis of this feature as squamous cell carcinoma is understandable. X63. (Fig. 16-3 from Batsakis, J.G., Hyams, V.J., and Morales, A.R. Special Tumors of the Head and Neck. American Society of Clinical Pathologists, 1983. Chicago, Illinois.)

and recurrence may result. It is also possible that some recurrences are actually new primary lesions, since approximately 10 percent of the patients may have multiple lesions in different parts of the body, either synchronously or metachronously.

Whether there exists a malignant granular cell tumor is conjectural and controversial. Most of the so-called examples reported in the literature are some form of an alveolar soft part sarcoma.

SCHWANNOMA

SYNONYMS AND RELATED TERMS: Neurilemoma; neurinoma.

Definition. The term schwannoma is used in an appropriate generic sense for tumors arising from the Schwann cell in peripheral and some cranial nerves. It embraces the clinicopathologic lesions called neurilemoma, neurofibroma, plexiform neurofibroma, and neurogenous sarcoma. The neurilemoma is a solitary and often encapsulated tumor, usually attached to or surrounded by a nerve, and is almost never associated with malignant change. It is only occasionally found in von Recklinghausen's disease. Nerve fibers rarely traverse the tumor and retrogressive changes, such as cystic alterations or hemorrhagic necrosis, are usually present. It has, in its classic presentation, an Antoni A and Antoni B microscopic appearance.

In contrast, the neurofibroma is nonencapsulated and often multiple. It is the characteristic neurogenous tumor of von Recklinghausen's disease. Neurites typically pass through the tumor and retrogressive changes are less common. Sarcomatous change has been said to occur in 5 to 15 percent of neurofibromas, with the larger percentage involving the classic von Recklinghausen's disease.

Because of these differences, the following discussion attempts to separate the neurofibroma from the neurilemoma.

Sites of Tumor. Although a multiplicity of major and minor nerves pass through or are distributed within the deep tissues of the anatomic region above the level of the clavicles and below the cranial cavity and could supply an ample source of neurogenous neoplasms, they are infrequently reported in the upper respiratory tract.

In the AFIP-OTR material (1976-1983), there were 30 patients with neurilemoma involving the nasal cavity; 5 involved the ethmoid sinuses; 1 of maxillary sinus origin; and 2 designated as sinonasal area only. There were 2 diagnosed as malignant neurilemomas, 1 each in the nasal cavity and sphenoidal sinus. In the same time period, the AFIP-OTR contained 6 patients with neurofibromas arising in the sinonasal tract, 4 from the nasal cavity and 2 not further identified as to origin.

Of the two forms, neurilemoma is the most often reported. The neurogenous sarcoma, on the other hand, is unusual in the nasal cavity, paranasal sinuses, and larynx.

Nasal Cavity. As of 1972, only seven patients with a neurilemoma primary in the nasal cavity had been reported in the English and foreign literature (Iwanura et al.). We believe this to be a considerable underestimation of the frequency of this group of tumors.

The olfactory nerve can safely be excluded as a possible nerve of origin in these cases, since it contains no Schwann cells.

The tumors may be firm, gelatinous, or cystic. Because of their resemblance to a nasal polyp, accurate diagnosis is not made until microscopic examination. Because of their expansile growth, pressure atrophy of adjacent bone may occur.

Paranasal Sinuses. In the paranasal sinuses, Schwann cell tumors arise from the ophthalmic and maxillary branches of the trigeminal nerve and branches of the autonomic nervous system. Robitaille and colleagues, after a review of the American and European literature from 1810 on, accepted 15 documented cases and added a case from their own experience. These lesions were classified as follows: 12 neurilemomas, 2 neurofibromas, 2 plexiform neurofibromas, and 1 neurogenous sarcoma. In one patient, the neurilemomas were multiple.

The age of the patients at the time of diagnosis ranged from 19 to 60 years, with a mean of 29 years. Men and women were nearly equally represented. Only two of the patients had Recklinghausen's neurofibromatosis.

The maxillary sinus was involved in 10 patients, ethmoid sinus in 8 patients, and the sphenoid sinus in 1 patient. Nasal extension occurred in 5 of the patients. In 3 patients, the orbit was breached. Only 5 of the tumors (nasal) were accessible to direct visualization and biopsy.

Clinical evidence of the tumors consisted of epistaxis, pain, nasal obstruction, and unilateral exophthalmos. Epistaxis was associated with ethmoidal and nasal fossa involvement, while pain occurred with maxillary sinus tumors.

Fourteen of the recorded lesions were benign and cured by excision. There were two local recurrences, one in a patient with neurofibromatosis. Only one tumor was biologically malignant with metastases. In this instance, the rare malignant transformation of a neurilemoma occurred.

Larynx. By 1969, 86 patients with primary Schwann cell tumors of the peripheral nerves of the larynx had been reported. In the AFIP-OTR (1976-1983), there were 7 neurilemomas, 3 neurofibromas, and 1 each of neurofibrosarcoma and malignant schwannoma reported arising in the larynx.

In the larynx, the tumors may present at any age (3 months to 75 years). They are most common in the third decade (Batsakis and Fox). The incidence in females exceeds that in males by a 2 to 1 ratio. The principal signs and symptoms are dyspnea, dysphonia, and dysphagia. The great majority of these neurogenous tumors originate either

from the aryepiglottic fold or the false cords. The lesions are usually solitary, lobulated, and, unless there has been prior surgical intervention, the overlying mucosa is intact. If the size is great, the mass may obscure the endolarynx, making it impossible to visualize the true cords.

Adequate removal has not been followed by recurrence. Neurogenous sarcomas of the larynx are rare. The larynx, like the upper airway, is infrequently involved in patients with multiple neurofibromatosis. Chang-Lo recorded the 20th case in 1977. All were neurofibromas.

Many of the reports have considered the neurofibromas and the neurilemoma as one entity and it is difficult to obtain differences in biologic behavior.

Trachea. The trachea is an unusual site for a Schwann cell tumor. Ma and associates recorded the eighth case in 1981. Five have been neurilemomas and three neurofibromas. None was associated with neurofibromatosis. As with other intraluminal tracheal tumors, airway obstruction compelled the patient to seek medical attention relatively early in the course of the disease. The AFIP-OTR material (1975-1983) revealed one neurilemoma and two neurofibromas as arising in the trachea.

Other Sites. Schwann cell tumors also may make their clinical presentation in the nasopharynx, pharynx, and larynx by external pressure signs and symptoms. The AFIP-OTR (1975-1983) revealed four neurilemomas, four neurofibromas, and four malignant neurilemomas arising in the parapharyngeal area. In the parapharyngeal space, Schwann cell tumors, predominantly, are among the most common lesions arising within that region. Their origin is from the vagus and cervical sympathetic nerves and they can range in size from 3 cm to extensive tumors extending from the mastoid process to the clavicle.

Acoustic neurilemomas will be discussed in the section on Tumors of the Ear.

Microscopic. Neurilemoma is an encapsulated tumor with a distinctive pattern formed by well developed cellular structures (Antoni type A tissue) which, on cross sections, produce a regimentation of nuclei in twisted rows of palisades (the Verocay body) (figs. 246, 247). These structures are embedded in a loose textured stroma in which the fibers and cells form no distinctive pattern (Antoni type B tissue). Retrogressive changes, including necrosis, cystic degeneration, lipidization, and angiomatous clusters of blood

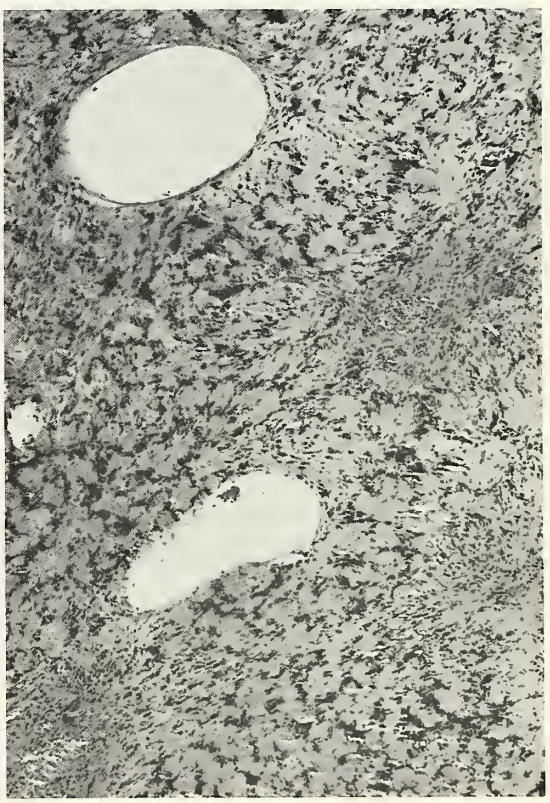

Figure 246
NEURILEMOMA
This neurilemoma of the sinonasal tract shows prominent vascularity and compact tissue (Antoni type A) with prominent palisading of the nuclei of the neoplastic cells. X63.

Figure 247
NEURILEMOMA
Note the palisading of the tumor nuclei with their orientation around foci of fibrous-like tissue, the so-called Verocay bodies. X160.

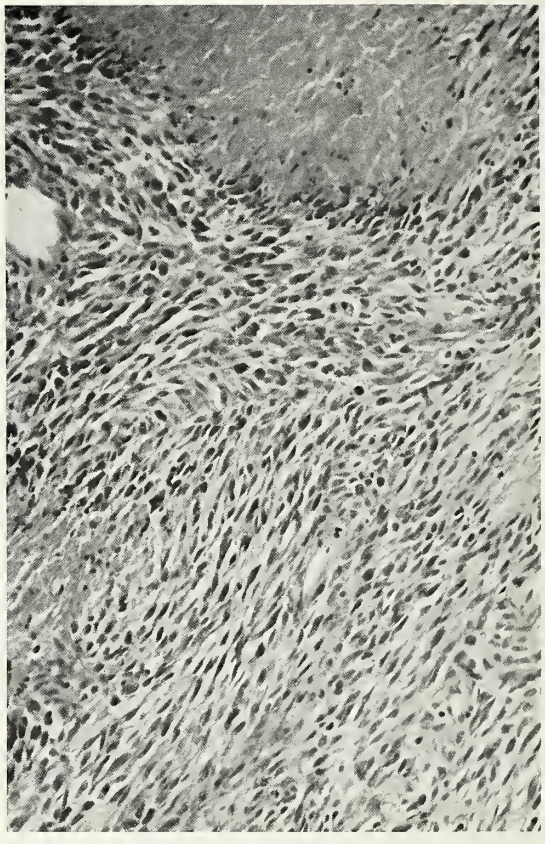

Figure 248
MALIGNANT NEURILEMOMA
A malignant neurilemoma of the temporal bone area with a malignant spindle cell morphology and areas of tumor necrosis. X160.

vessels with focal thrombosis are prominent and do not bear relation to the size or location of the tumor. The Antoni B pattern is commonly intermixed with the Antoni type A pattern, but an entire tumor may have this Antoni type B pattern arrangement. In this latter histologic variant of the neurilemoma, the important diagnostic features are the collection of dilated blood vessels with thickened hyaline walls, perivascular hyaline deposits, and fibrous thrombi. Areas of recent and old hemorrhage also may be common. Malignant degeneration (fig. 248) is rare.

Neurofibromas are nonencapsulated and manifest a spindle cell pattern of growth (figs. 249, 250). They lack the many retrogressive foci seen in the neurilemoma and the cells commonly manifest serpentine nuclei. Vascular proliferation and associated vascular changes are not commonly seen. Areas of nerve tissue are commonly present in association with the fibrous structure of the neurofibroma. Plexiform neurofibromas are the result of growth within and about a nerve, giving the nerve trunk a tortuous, thickened, and plexiform appearance.

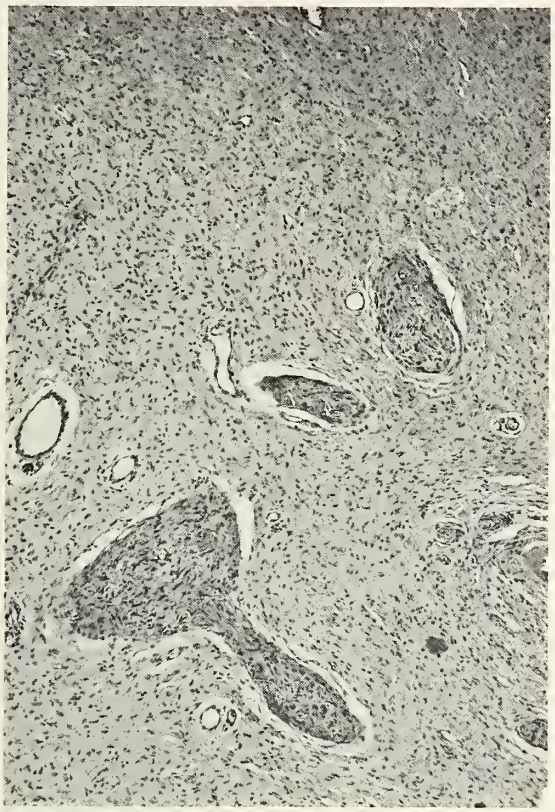

Figure 249
(Figures 249 and 250 are from the same patient)
NEUROFIBROMA
This neurofibroma of the maxillary sinus exhibits the peripheral nerve structures transversing the proliferating neoplastic cells. X63.

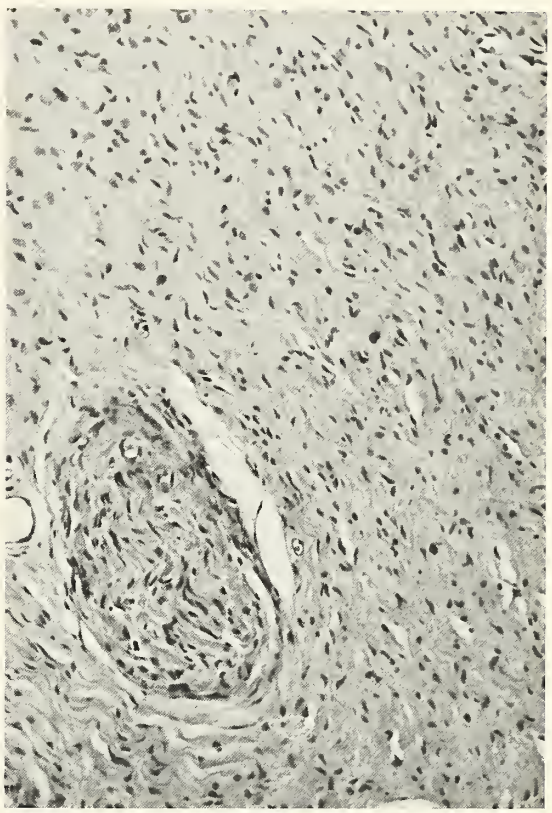

Figure 250
NEUROFIBROMA
Note the normal histology of the peripheral nerve and the neoplastic proliferation of the delicate Schwann-like cells without the nuclear palisading of the neurilemoma. X160.

Otolaryngologic Manifestations of von Recklinghausen's Disease. The neurocutaneous, autosomal dominant hereditary disorder, von Recklinghausen's disease, has multiple forms of presentation in the head and neck (Holt).

Erosion and enlargement of cranial nerve foramina may be seen, with optic gliomas and acoustic neuromas being common. A neurofibroma of the trigeminal nerve is commonly manifested by enlargement of the foramen ovale or, if the Gasserian ganglion is involved, an erosive enlargement of the superior orbital fissure is noted.

Microcephaly, with skull bosses in the frontal and temporal regions, can be seen clinically and radiographically. There may be a partial or complete absence of the greater or lesser wings of the sphenoid bone. An intraorbital neurofibroma may so influence bone growth that an ipsilateral hypoplasia of the maxillary and ethmoid sinuses may occur.

The acoustic neuroma is the most common intracranial tumor in the adult with von Recklinghausen's disease and it is most frequently seen in cases with minimal subcutaneous manifestations of the disease. It

is bilateral in over 80 percent of cases. When bilateral acoustic neuromas occur in children, it is almost always associated with this disease.

Schwann cell tumors and meningiomas have been reported along the entire length of the facial nerve, especially the intratympanic portion. Occurrence in the middle ear can also be caused by involvement of Jacobson's or Arnold's nerve.

Most of the reported cases of paranasal sinus involvement have been secondary to peripheral nerve sheath tumors of the orbit with encroachment on the maxillary or ethmoid sinuses. Involvement of the floor of the orbit and pterygomaxillary space is common.

Deformities of the facial bones is common and may include one or more of the following: asymmetry; hypertrophy; atrophy; radiolucent bone defects; and cysts. Intraosseous neurilemomas of the facial bones are rare, but both mandible and maxilla may be involved. Such lesions may present as localized facial swelling overlying an expanding mass. A wide mandibular canal or mental foramen may be caused by expanding neurofibroma.

Schwann cell tumors in the facial soft tissues may interfere with the nasal airway, lid excursion, and mastication. The plexiform neurofibroma may grow to disfiguring proportions with an "elephantiasis" presentation.

TRAUMATIC NEUROMA

These nonneoplastic lesions are the result of either amputation or trauma to a nerve. They are a manifestation of a biologic frustration in nature's attempt to rehabilitate the nerve by regrowth and regeneration.

Gross. Traumatic neuromas are generally oval or oblong and gray, white, firm and rubbery, and circumscribed, but not encapsulated. They rarely exceed 2.0 cm in dimension. They have a dense fibrous appearance, little vascularity, and a non-uniform disposition of nerve fibers. In some instances, a nerve terminates at the upper pole of the mass, in others the nerve fibers spread and become incorporated with the fibrous elements of the neuroma. The mass is usually at the amputation site or at the site of trauma, but it may be situated several centimeters above the site of injury.

Microscopic. Histologically, these lesions consist of tangled and interwoven proliferations of endoneural and perineural connective tissue, Schwann cells, and regenerating neuraxes. The amount and density of the external resistance determines the size and shape of the neuroma. With aging, there is scarring and contraction of the neuroma.

Frequency and Sites. Considering the number of nerves that are cut and traumatized in surgical procedures in the head and neck, traumatic neuromas are distinctly unusual. Very likely they exist in greater numbers, but in a subclinical status.

The oral and perioral regions are areas of predilection, but they can be manifest in any part of the airway if regional nerves have been transected.

TUMORS DERIVED FROM THE DIFFUSE NEUROENDOCRINE SYSTEM

The diffuse neuroendocrine system (DNES) is composed of central and peripheral divisions. Recent embryologic, experimental, and morphologic studies have challenged the common (neural crest) ancestral origin for cells in the DNES. It is now likely that the various cells are of diverse origin even though they have developed a similar set of biochemical characteristics. If there is a common progenitor, it is the embryonic

epiblast. Regardless of their location or origin from a particular germ layer, all cells of the DNES are neuroendocrine programmed.

In the head and neck, medullary carcinoma of the thyroid gland and the paraganglioma are the most commonly encountered tumors of the DNES. Considerably less often does the pathologist find other tumors of neuroendocrine derivation (carcinoids and oat cell carcinoma) in the upper respiratory tract and salivary tissues.

Pathogenesis. Their cell of origin is debatable, but argyrophilic cells are found sparsely distributed among epithelial cells of the bronchi and bronchioles. Here their relationship to other bronchial cells is similar to that between melanocytes and other epidermal cells of skin. Like cells have also been demonstrated in the larynx of guinea pigs and rats and the identification of neoplasms with light and electron optic characteristics of oat cell carcinomas in the larynx points to the presence of similar cells in humans. Argyrophilic cells are also present in the ectodermally derived salivary glands, oral cavity, pharynx, and sinonasal tract.

Argyrophilia, in itself, is not conclusive evidence of neuroectodermal origin, and evidence is collecting to support endocrine-type differentiation from "indifferent" cells in mucosa, perhaps influenced by microenvironmental factors (McDowell et al.).

The most recognizable neoplastic derivatives of these cells are carcinoid and oat cell carcinomas, both of which are unusual in the upper aerodigestive tracts. Even less often, cells containing endocrine granules comprise a portion of an adenocarcinoma, often with "intestinal" features. Other examples have features shared by both oat cell carcinoma and "classic" carcinoids.

That all neoplasms with a histologic pattern and cytologic characteristics of oat cell carcinoma may not be derived from neuroendocrine-type cells has been clearly shown by electron microscopic evaluation. In many purported examples, the lack of documentation beyond hematoxylin and eosin examination excludes them from consideration. The demonstration of argyrophilia is a helpful step, but this reaction is dependent not only on technic but also on the number and nature of granules within the cells' cytoplasm. Electron microscopic identification and verification of neurosecretory type granules is essential for definition.

SMALL (OAT) CELL CARCINOMA

In 1972, Koss and associates reported 14 "small (oat) cell carcinomas" from a series of 492 cases of neoplasms of minor salivary gland origin, an incidence of 2.9 percent. The hard and soft palate were the primary sites in 4 cases; the tonsils in 3; base of tongue in 2; nasal cavity or paranasal sinuses (antrum and ethmoid) in 4; and the epiglottis in 1. By early 1980, 15 purported examples of oat cell carcinoma of the larynx had been recorded. Of the total of 29 cases, only 8 (all laryngeal) had electron microscopic confirmation of the neuroendocrine nature of the neoplastic cells. None of the cases reported by Koss and associates and only seven of the laryngeal oat cell lesions were examined by technics designed to demonstrate argyrophilic granules. In the 18 cases of small cell (oat cell) carcinoma of the larynx reported by Gnepp and colleagues, half had a Grimelius stain performed with negative results. Two cases studied by electron microscopy did reveal neurosecretory intracytoplasmic granules.

With the increasing use of electron microscopy on head and neck tumors, it is predicted that neuroendocrine components will be found in a variety of neoplasms. To

date, however, the cases are few in number (Eusebi et al.).

Nasal Cavity. In the nasal cavity, these tumors can present as poorly differentiated carcinoma with alveolar patterns (Kameya et al.), as oat cell type carcinoma, or as primary adenocarcinoma of so-called enteric type (Schmid et al.). In the cases reported by Kameya and associates, two patients had systemic evidence of abnormal endocrine secretion (e.g., high serum calcitonin, cortisol).

Larynx. In the larynx, neuroendocrine carcinomas have been almost exclusively of the undifferentiated small cell type, Carcinoids of the larynx are exceptionally rare (Mullins et al.).

The primary oat cell carcinoma of the larynx is usually a supraglottic, submucosal tumor. The epiglottis and false cords appear to be sites of predilection. Subglottic carcinomas have also been reported. Their size has varied from 2 cm to large tumors infiltrating the entire hemilarynx and subglottis.

There is no apparent sex predilection and the patients are almost always in their late fifties to seventies.

Microscopic. There is no transition zone from the surface epithelium of the larynx and an infiltrating poorly differentiated carcinoma (figs. 84, 85). The tumor usually fills the submucosa and is composed of sheets and cords or clusters of closely packed small cells with scant cytoplasm and round to oval hyperchromatic nuclei without prominent nucleoli. Focal areas of necrosis are usually present, and a high mitotic rate can be seen in any area. More spindle cell zones and abortive attempts at lumen formation are also present. Argyrophilic (Grimelius) silver stains are variable in their reaction.

Ultrastructural examination reveals tumor cells that vary moderately in size and shape. The cytoplasm usually contains abundant clusters of polyribosomes with poorly developed rough endoplasmic reticulum. Many, but not all, of the tumor cells contain numerous cytoplasmic membrane-bound granules with a central electron dense core separated from the limiting membrane by a clear zone. The granules are similar, if not identical, to those described in tumors of the amine precursor uptake and decarboxylation (APUD) system (Mullins et al.).

Prognosis. The overall prognosis for extrapulmonary oat cell carcinomas, including those of the larynx, using standard treatment modalities is grave. The use of aggressive therapy combining radiotherapy with multidrug systemic chemotherapy appears indicated.

There are occasional long-term survivors, but most patients die in less than two years with nodal and systemic metastases.

Extra-adrenal paragangliomas and extracranial meningiomas of the upper respiratory tract are discussed in the section on Tumors of the Ear.

SYMPATHETIC NEUROBLASTOMA AND GANGLIONEUROMA

No more than 5 percent of all neuroblastomas take their origin from the sympathetic and other neuroectodermal tissue of the head and neck. Metastatic neuroblastoma must always be considered in the differential diagnosis.

Metastatic Neuroblastoma. If the skull bones are excluded, metastatic neuroblastoma from a distal primary site below the clavicle to facial bones is very unusual. Only nine patients had been reported by 1976 (Snyder and Cawson). All secondary jaw lesions occurred in children under the age of 8 years. The maxilla was involved only

once, while the most commonly affected sites were the molar region and the angle of the mandible. Jaw metastases are accompanied by widespread, systemic involvement of all patients.

PRIMARY NEUROBLASTOMA (Excluding Olfactory Neuroblastoma)

All histologic subtypes of neuroblastoma may be primary in the head and neck, but are unusual lesions in the intrinsic airway. The differentiation ranges from the least differentiated form, the sympathicogonioma, through the differentiated ganglioneuroma. Intermediate forms are the sympathicoblastoma and the partially differentiated ganglioneuroblastoma.

Sites of Tumor. Apart from the cervical sympathetic chain, these tumors have arisen in the larynx, pharynx, nodose ganglion of the vagus nerve, infraorbital nerve, and tongue (Todd and Brooks).

Involvement of the airway, however, is usually a secondary one from a cervical sympathetic chain tumor. Horner's syndrome, dyspnea, dysphagia, and stridor are signs and symptoms produced as the tumors encroach on the aerodigestive tract. Rare tumors may be functional (catecholamine-secreting).

Age Distribution. Ganglioneuromas in the head and neck present over a wide age range (2½ to 88 years), but the largest concentration is in the first decade of life. On rare occasions, von Recklinghausen's disease may be present.

Gross. The ganglioneuroma is usually circumscribed and appears encapsulated. Extensions from the main tumor may involve adjacent structures. The tumors are firm and have a pearly gray parenchyma. Calcification may be present.

Microscopic. It has been appreciated that neuroblastomas of the head and neck have a higher degree of maturation than abdominal or adrenal counterparts. In that light, the ganglioneuroma has been cited as the most common form of these tumors in the head and neck.

The fully differentiated ganglioneuroma is benign and composed entirely of adult ganglion cells with or without satellites, set singly or in groups in a matrix composed of neurites with schwannian sheaths and inconspicuous fibrous support framework (fig. 251).

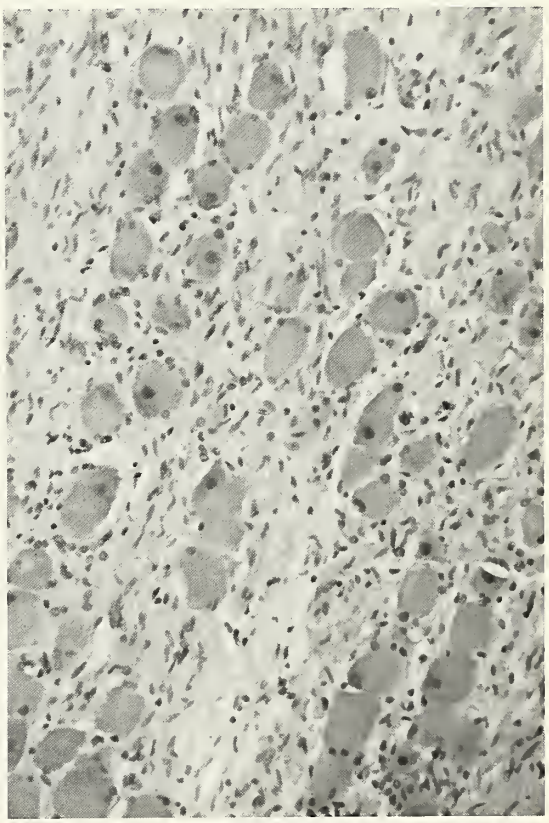

Figure 251
GANGLIONEUROMA
This ganglioneuroma of the pharynx consists of adult ganglion cells with satellite cells in a matrix composed of neurites with schwannian sheaths and inconspicuous fibrous supporting framework. X160.

Aside from the local attachments of the tumor, the ganglioneuroma is biologically benign. The presence of undifferentiated or partially differentiated foci in the tumor alters this assessment. The partially differentiated tumor, ganglioneuroblastoma, is, however, unusual in the neck.

OLFACTORY NEUROBLASTOMA

SYNONYMS AND RELATED TERMS: Olfactory esthesioneuroepithelioma; olfactory esthesioneurocytoma; olfactory esthesioneuroblastoma; olfactory placode tumor; primary intranasal neuroblastoma; nasal sympathioma.

Definition. Olfactory neuroblastoma is an uncommon, malignant, aggressive neoplasm of neural crest origin capable of metastatic behavior. Clinically and histologically, the neoplasm appears to take origin from the olfactory membrane of the sinonasal tract. It is characterized by organoid masses of primitive neurocytoblasts with neural fibrils, but no ganglion cells.

Frequency and Age. Approximately 200 cases of these olfactory neoplasms have been described in the medical literature since the first case report by Berger and associates in 1924 introduced the tumor entity. The AFIP-OTR contains approximately 200 cases contributed over a 40-year period. The medical literature and the AFIP-OTR material demonstrate a slight female predominance. The ages at onset ranged from 3 years to the mid-ninth decade, with a bimodal peak in the second and sixth decades, but with no racial predilection.

Histogenesis. There have been several theories as to the site of origin of the olfactory neuroblastoma (Schall and Lineback). Jacobson's organ (vomeronasal organ), sphenopalatine (pterygoid palatine) ganglion, olfactory placode, and the ganglion of Loci (nervus terminalis) have all had their proponents, but these ideas have not been convincing on either an anatomic or clinicopathologic basis. Experience has supported overwhelmingly the olfactory membrane of the upper nasal cavity area as the organ of origin (Shah and Feghali). The clinical presentation of the olfactory neuroblastoma, essentially in the upper or roof of the nasal cavity, is convincing evidence. The infrequent presentation in the lower lateral nasal cavity or the maxillary antrum can be explained by the rare finding of ectopic olfactory membrane in these areas (Church and Uhler). Light microscopic and ultramicroscopic studies (Chaudhry et al.) support the bipolar neurons of the olfactory membrane as the neoplastic cell. The role of the supporting or sustentacular cells of the olfactory membrane in the neoplasm is undecided, but they may have an occasional role.

Etiology. Herrold was able to produce olfactory neuroblastoma-like neoplasms of the olfactory membrane area in hamsters following subcutaneous injection of the carcinogen dimethylnitrosamine. No evidence at this time has linked the environment with the cause of human olfactory neuroblastoma.

Gross. The most common gross presentation is a glistening, mucosal covered, soft gray to pink to brown, polypoid mass, sometimes friable and showing bleeding on manipulation in vivo. The size is difficult to accurately assess because the size limitation of the nasal cavity prevents the formation of an exceptionally large mass and, also, the local tissue infiltration and invasion is not appreciated in the gross specimen. The neoplasm may vary from a small nodule less than 1 cm to a mass filling the bilateral nasal cavities and possibly extending into adjacent paranasal sinuses and nasopharynx and also

infiltrating intervening or adjacent tissue. Occasionally there is a gritty (green pear) sensation on sectioning the tumor mass.

Microscopic. The olfactory neuroblastoma presents an agreed overall neural neoplastic structure. There are those who feel that there should be microscopic subdivisions because of clinicopathologic correlation with certain histologic features (Berger et al.; Gerard-Marchant and Micheau; Mendeloff). Others feel that there is no correlation between histologic structural variation and clinical behavior, proposed treatment, or prognosis (Hutter et al.; Bailey and Barton). The large number and amount of patient material in the AFIP-OTR has afforded an opportunity to test the advisability of a microscopic subclassification (Richardson and Hyams). This study supports subclassification and the results are presented on page 248. The terminology olfactory neuroblastoma is selected because of the relative ease of pronunciation and recall compared to the other tongue twister designations that have been proposed.

Olfactory Neuroblastoma, Grade I. This group (figs. 252-255) is the most differentiated of the four grades. Common to the whole spectrum of olfactory neuroblastomas, there is a definite lobular architecture, and

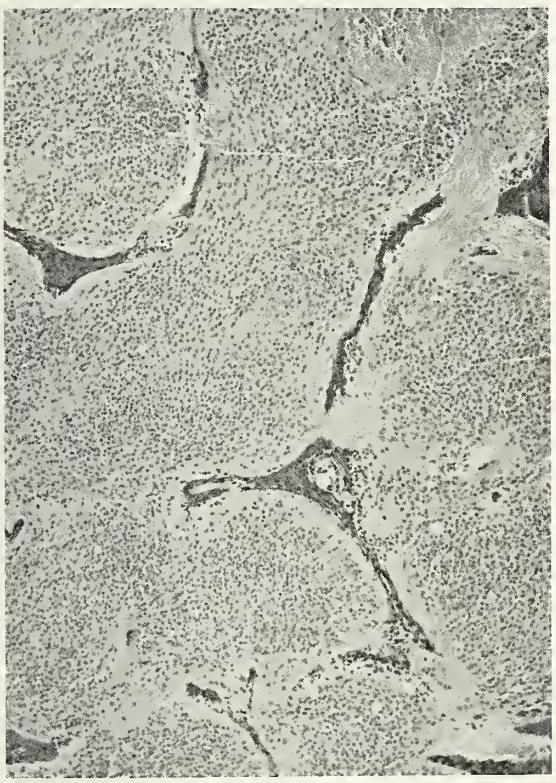

Figure 252
(Figures 252-255 are from the same patient)
OLFACTORY NEUROBLASTOMA (GRADE I)
This grade I olfactory neuroblastoma of the upper nasal cavity has a lobular architecture with a vascular interlobular fibrous stroma. X63.

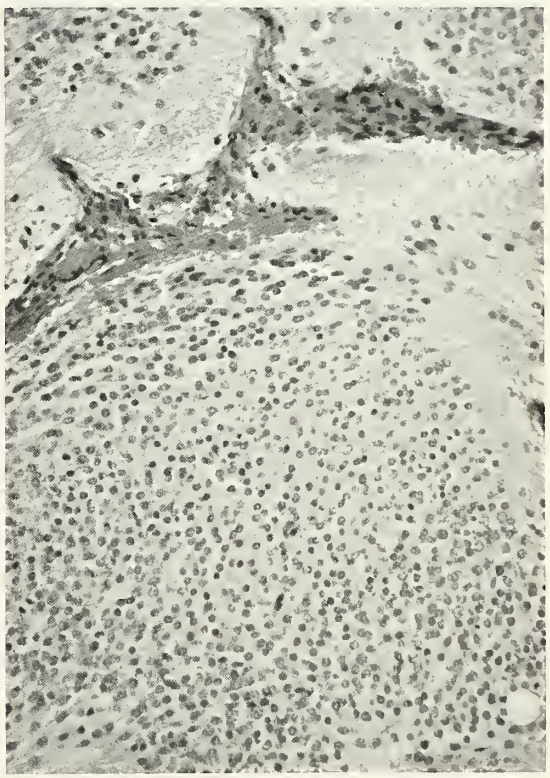

Figure 253
OLFACTORY NEUROBLASTOMA (GRADE I)
Note the interconnection between the lobules via the glial-like stroma and the uniformity of the neoplastic cellular element. X160.

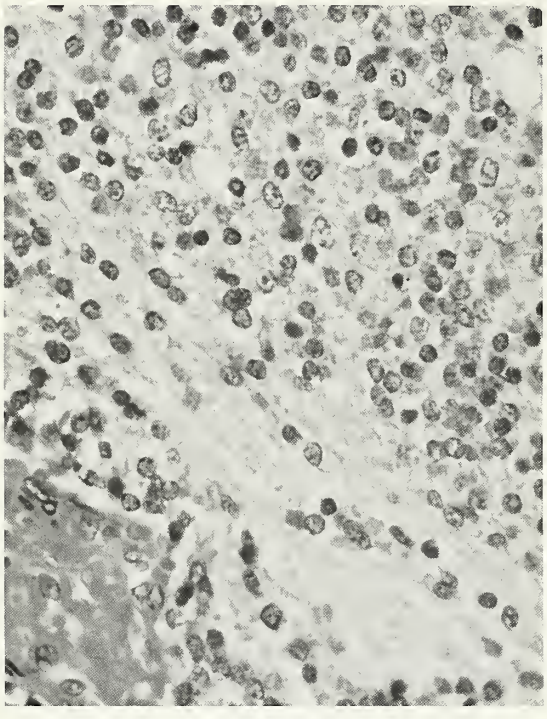

Figure 254
OLFACTORY NEUROBLASTOMA (GRADE I)
Note the uniform nonmitotic histologic character of the neoplastic cell nuclei and the suggestion of glial-like stroma representing the cell cytoplasm. X400.

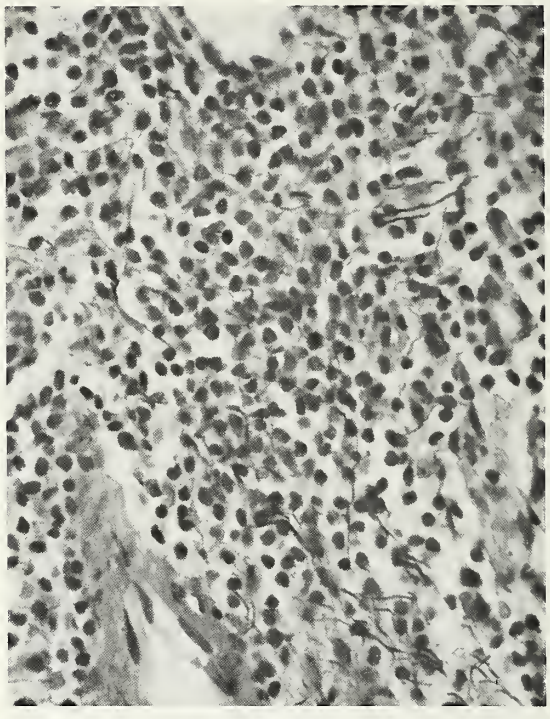

Figure 255
OLFACTORY NEUROBLASTOMA (GRADE I)
A Bodian stained section illustrates axon fibers. X400.

in this grade I histology, there is a distinct tumor intercommunication between lobules. The interlobular fibrous stroma is quite often extremely vascular, at times suggesting the diagnosis of a hemangiomatous neoplasm. The particular distinctive microscopic finding in this grade is the extremely good differentiation of the neoplastic cells, with a uniform round to vesicular nucleus of varying chromaticity, with or without nucleoli. No mitotic activity is seen. The neoplastic cell usually does not have a distinct cytoplasmic border, but rather the nucleus is surrounded by an intermixing neurofibrillary material which suggests a cytoplasmic extension. The Bodian histochemical stain demonstrating prominent axon fibrils supports this idea. Frequently the nuclei and neurofibrillary material will form a pseudorosette pattern (Homer Wright rosettes). Varying amounts of calcification may be noted, accounting for the occasional gritty gross character. Necrosis is absent.

Olfactory Neuroblastoma, Grade II. This group (figs. 256-259), and the grade I previously described, have been considered olfactory esthesioneurocytomas (Berger et al.) Gerard-Marchant and Micheau; Mendeloff). In the AFIP-OTR data, the majority of the olfactory neuroblastomas are in this grade II group. The grade II olfactory neuroblastoma has a less optimistic outlook than the more

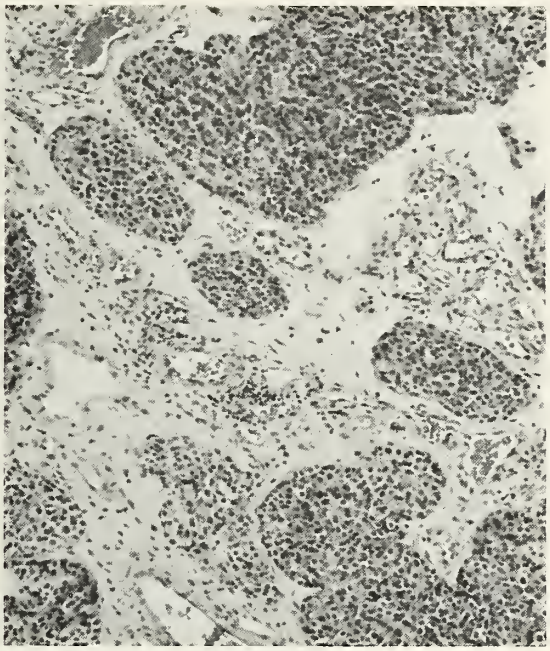

Figure 256
OLFACTORY NEUROBLASTOMA (GRADE II)
This grade II olfactory neuroblastoma from the upper nasal cavity also has the lobular architectural pattern seen in the previous illustrations. X50.

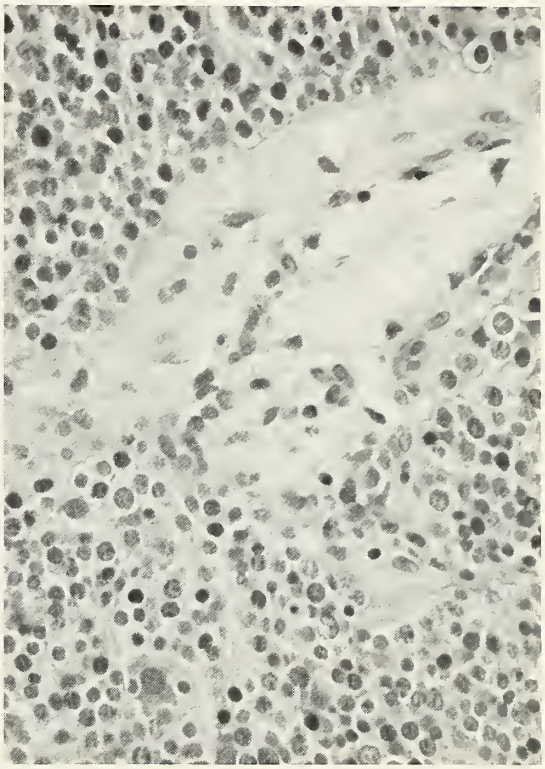

Figure 257
OLFACTORY NEUROBLASTOMA (GRADE II)
There is an increase in pleomorphism of the neoplastic cell nucleus, with less definition of the glial stroma than seen in the grade I olfactory neuroblastoma. Occasional mitosis is not unusual. X400.

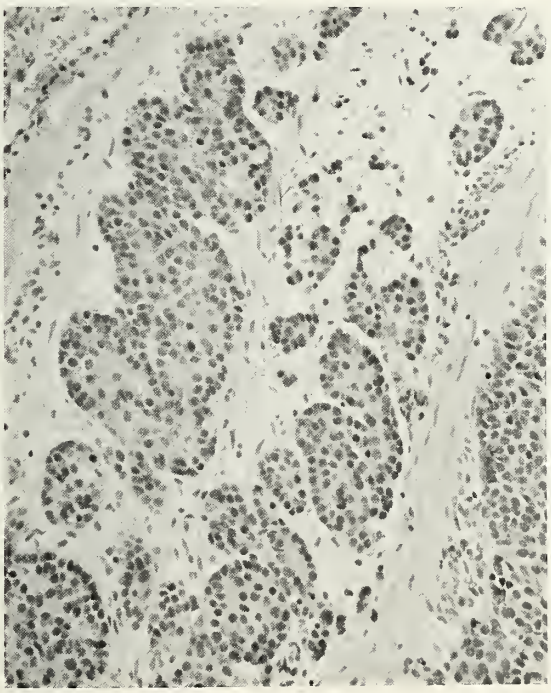

Figure 258
OLFACTORY NEUROBLASTOMA (GRADE II)
In the grades I and II olfactory neuroblastomas, a common finding is the forming of pseudorosettes (Homer Wright rosettes) consisting of a glandlike arrangement of tumor cells with cellular cytoplasm forming the space. X160.

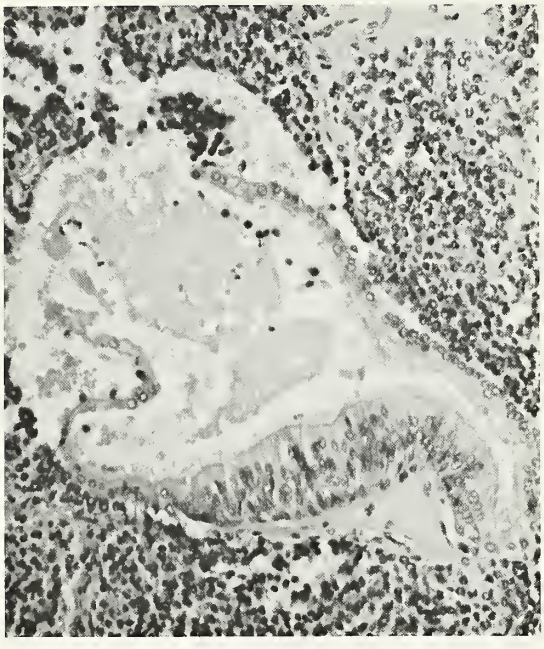

Figure 259
OLFACTORY NEUROBLASTOMA (GRADE II)
The occasional glandlike structure seen in this grade II olfactory neuroblastoma has led to the designation of neuroendocrine carcinoma. The authors (VJH) feel this reclassification is excessive and that these glands may merely represent the participation of neuroectodermal supporting cells from the olfactory mucosa or the underlying Bowman's glands in the tumor process. X160.

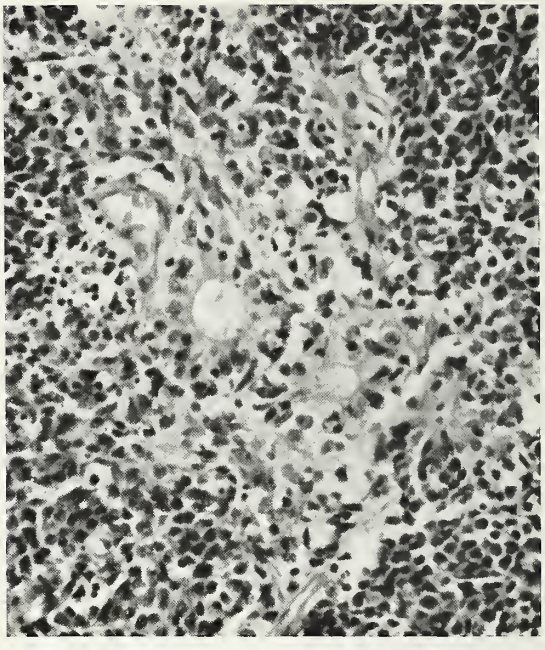

Figure 260
OLFACTORY NEUROBLASTOMA (GRADE III)
In this grade III olfactory neuroblastoma of the nasal cavity, note the anaplastic neoplastic cell and, in addition, the prominent true (Flexner-Wintersteiner) rosettes. X160.

well differentiated olfactory neuroblastoma grade I. The lobular communicating architecture is retained with a usually prominent vascularized stroma. The neurofibrillar element is present, but less well defined, while the distinguishing feature is the increased anaplastic appearance of the nuclei. Mitotic activity can be seen. There is a moderate amount of nuclear anaplasia and some cytologic primitiveness suggested by an occasional cytoplasmic rim. Pseudorosettes and calcification can still be seen and necrosis is absent. The demonstration of axons by the Bodian histochemical method was somewhat more difficult than in the grade I neoplasm. Glandlike structures are seen not infrequently. Whether these glands represent participation of the olfactory mucosal supporting cells, basal cells, or Bowman' glands (all of which are probably of neuroectodermal origin), or whether they are an intermixture with mucoserous glands of the anatomic area, is not settled. The supporting cell choice seems most likely.

Olfactory Neuroblastoma, Grade III. This histologic type (fig. 260) has been labeled as olfactory esthesioneuroepithelioma by Berger and associates, Gerard-Marchant and Micheau, and Mendeloff, and was recognized by them as cytologically and clinically a more aggressive neoplasm. The characteristic histology still retains a suggestion of a lobular architecture with an interstitial vascular stroma. There is a hypercellularity of the neoplastic cell proliferation with the individual cell being more anaplastic, hyperchromatic, and having increased mitotic ac-

tivity. The neurofibrillar component is difficult to delineate. The microscopic characteristic of this grade III group is the inclusion of structures resembling true neural rosettes (Flexner-Wintersteiner type). Occasionally, these so-called true neural rosettes may resemble glandlike structures and there is speculation as to whether they might be formed by the supporting or sustentacular cells of the olfactory membrane (Gerard-Marchant and Micheau). Axon fibers are not usually demonstrated by special histochemical technics. Calcification is absent, but necrosis may occur. An orientation of neoplastic cells around vessels (vascular rosettes) may be seen focally in any of the three previous cytologic grades.

Olfactory Neuroblastoma, Grade IV. This group (figs. 261-263) represents the most undifferentiated cytology and has been categorized in the literature as an olfactory esthesioneuroblastoma (Gerard-Marchant and Micheau). This subtype will be the most difficult to distinguish, by light microscopy, from small cell undifferentiated malignancies seen in the sinonasal tract area. The overall lobular architecture may be retained and the neoplastic element is a more undifferentiated, anaplastic, hyperchromatic nucleus with prominent mitotic activity. The cytoplasm is indistinct and difficult at times to associate with a neural origin. Electron microscopic examination is usually the most reliable proof of cell type. No true or pseudorosettes are seen in this group. There are no axons demonstrated by special histologic technics and calcification does not occur, but necrosis might be quite common.

Special Histologic Technics. In addition to the special stains mentioned in the subclassifications, neural histochemical procedures are consistent with a neuroectodermal derived neoplasm. Of interest is the finding, in several cases contained in the AFIP-OTR, of

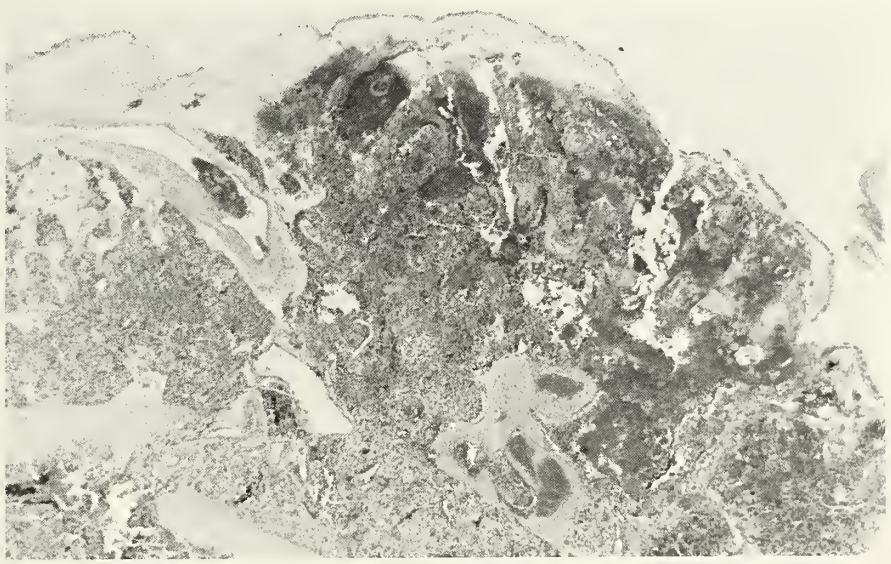

Figure 261
(Figures 261-263 are from the same patient)
OLFACTORY NEUROBLASTOMA (GRADE IV)
This grade IV olfactory neuroblastoma of the upper nasal cavity is the most undifferentiated of this neoplastic entity and the most difficult to identify histologically as olfactory neuroblastoma. A suggestion of the lobular pattern is present. X25.

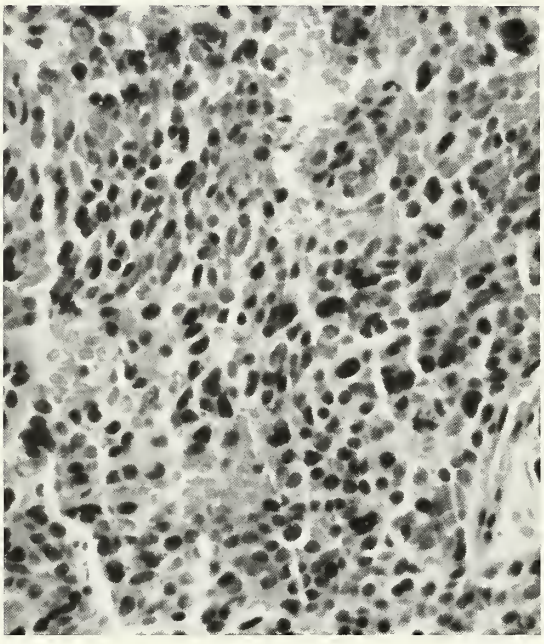

Figure 262
OLFACTORY NEUROBLASTOMA (GRADE IV)
Note the increased anaplasia of the neoplastic cell. No rosette structures are seen in this high-grade lesion. X160.

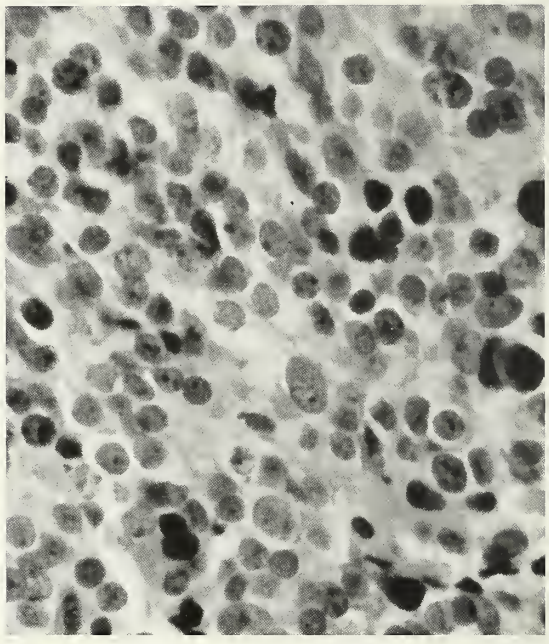

Figure 263
OLFACTORY NEUROBLASTOMA (GRADE IV)
This emphasizes the increased anaplasia of this type of olfactory neuroblastoma. The use of electron microscopy may be needed to assure the neural genesis of this lesion. X400.

brown pigment granules among tumor cells that reacted positive with the Fontana stain, but with further differential studies were felt to represent neural lipofuscin. The Grimelius stain has been consistently positive, demonstrating neurosecretory granules in the olfactory neuroblastoma, and this occurrence substantiates this tumor as being included in the APUD tumor concept (Chaudhry et al.). Positive fume-induced fluorescence on frozen sections is positive (Judge et al.). Ultrastructurally, the neoplastic cells in olfactory neuroblastoma are characterized by the presence of neurocytic processes and cytoplasmic neurosecretory granules (Chaudhry et al.; Taxy and Hidvegi).

Dr. J.C. Durham of AFIP, in his investigation of AFIP-OTR olfactory neuroblastomas by immunohistochemical analysis, found neuron specific enolase (NSE), S100 protein, chromogranin, and Leu-7 positivity in the majority of case material examined. Forty percent of his case material revealed a positive keratin reaction. He felt that the morphologic pattern of decoration was important. Neuron specific enolase positivity was diffuse and commonly intense in the olfactory neuroblastomas and acted as a preliminary neural tissue screener. The most diagnostic pattern was in the peripheral areas of the tumor lobules where a netlike positive staining with S100 protein of the modified Schwann-like cells occurred with or without the delicate intracytoplasmic random staining of granules with chromogranin. The finding of some neoplastic cellular positivity to cytokeratin and Leu-7 is not clearly understood and further investigation of the phenomena is needed.

Differential Diagnosis. Undifferentiated or poorly differentiated carcinoma is the most common choice on the list of differential diagnoses submitted by contributors of cases of olfactory neuroblastoma contained in the AFIP-OTR. The better differentiated olfactory neuroblastoma should not pose a diagnostic problem. Identification of the poorer grades (III, IV), however, may require the utilization of ultrastructural, immunoperoxidase, or fume-fluorescence studies. The neuroblastoma of nonolfactory areas may cause a differential problem either as a primary or metastatic neoplasm. However, the clinical setting, especially age, prognosis, and metastatic pattern, as well as the particular histologic appearance should serve to delineate the olfactory neuroblastoma as a unique neuroectoneural neoplastic entity. Other diagnoses submitted with cases of diagnosed olfactory neuroblastoma in the AFIP-OTR were embryonal and undifferentiated sarcoma, malignant vascular neoplasia, melanoma, lymphoma, plasmacytoma, anaplastic adenocarcinoma, Ewing's sarcoma, meningioma, extra-adrenal paraganglioma, pituitary adenoma, ependymoma, and chordoma.

The Neuroendocrine Carcinoma Controversy. Silva and associates presented a series of 20 cases of an upper nasal cavity neoplastic process that clinically had all the earmarks of olfactory neuroblastoma and the histology and clinical behavior essentially of the grade II group discussed above. The median age of this group was 50 years and the same sex and racial preference persisted. The light histology, ultrastructural examination, and special neuroendocrine studies paralleled those for olfactory neuroblastoma. The therapeutic approach and prognosis were essentially those of a grade II olfactory neuroblastoma. Because of the appearance of tumor cells arising from subsurface mucosal and glandular structures, Silver and colleagues proposed the term neuroendocrine carcinoma for this group of tumors. Such an addition to an already confused spectrum of sinonasal neoplasia seems unnecessary and certainly does not appear to benefit the understanding of the disease nor the outcome of the patient. These glandlike structures utilized in the argument for the diagnosis of neuroendocrine carcinoma have been noted in olfactory neuroblastomas. If they are truly part of the neoplasm, they could well be formed from the olfactory supporting cell which is felt to be neuroectodermal in origin and capable of secretory activity. The participation by Bowman's glands of the olfactory submucosal area (which are also thought to be of neuroendocrine origin) could also possibly account for this finding. The possibility of intermixed mucoserous glands of the nasal cavity area is another possibility.

Clinical. The main presenting symptoms in equal frequency were nasal obstruction or epistaxis, and almost as common was the combined presentation of both. Lesser manifestations were anosmia, headache, and ocular disturbances. The more undifferentiated the olfactory neuroblastoma, the shorter symptom time prior to diagnosis. Those patients without early medical consultation and, particularly, those with a high-grade histology may present facial deformity and proptosis. Kadish and associates and Elkon and associates have described a clinical grading which has correlated well with post therapy survival. Group A tumors were confined to the nasal cavity (89 to 100 percent, three-year survival). Group B involved the nasal cavity and paranasal sinuses (80 to 83 percent, three-year survival). Group C tumors spread beyond the confines of the nasal cavity and paranasal sinuses either

directly or by regional or distal metastases (40 to 53 percent, three-year survival).

An elevated excretion of vanillylmandelic acid (VMA) and homovanillic acid (HVA) has not been reported in olfactory neuroblastoma. Micheau demonstrated catecholamines in low concentration in six patients, but his determinations of VMA, HVA, and dopamine were of questionable value.

Radiographic Diagnostic Findings. Burke and colleagues found that the radiographic findings of nasal and paranasal sinus opacification and bone erosion in olfactory neuroblastoma are the same as in other aggressive neoplasms of the sinonasal tract area. Angiography frequently demonstrates hypervascularity and its utilization should be considered whenever there is suggestion of intracranial extension on laminagraphy without confirmation on CT scan.

Metastases. The majority of olfactory neuroblastomas behave essentially as local aggressors and mainly involve adjacent vital cavities, such as the orbit and cranial cavity. An estimated 20 to 42 percent exhibit metastasis to regional lymph nodes, lungs, and bone. In the AFIP-OTR material, all histologic grades may have metastasized locally or distally.

Treatment. Overwhelmingly, the therapeutic choice has been radical surgical excision followed by a planned, full-course, radiation regime (Baker et al.). There has been occasional success with either therapeutic modality utilized separately, and Walters and associates reported some success with chemotherapy administration for disseminated olfactory neuroblastoma.

Prognosis. Survival figures will vary depending upon the clinical staging of the olfactory neuroblastoma (Elkon et al.; Kadish et al.), as well as the histologic grade of the neoplasm (Gerard-Marchant and Micheau; Mendeloff). A review of the literature confirms a five-year survival of 50 percent, with or without residual neoplasm. Richardson and Hyams selected 50 patients of olfactory neuroblastoma from the AFIP-OTR material that furnished sufficient histologic material as well as meaningful follow-up information. Without knowledge of the clinical history in the individual patient, each case was histologically graded according to the schema proposed above. The average follow-up time was five years, and those cases lost to followup had at least two years post-treatment information. The therapy was radical surgery with planned pre- or postoperative radiation. The results for each histologic grade were: grade I, 6 patients had no evidence of disease, with 1 patient lost to followup; grade II, 19 patients had no evidence of disease, 3 patients died of disease, 3 patients died of intercurrent disease, and 4 patients were lost to followup; grade III, 5 patients had no evidence of disease and 6 patients died of disease; grade IV, all patients (4) died of disease.

The histologic grading information, together with the clinical staging described above, should certainly be a good prognosticator.

MALIGNANT MELANOMA

Malignant melanoma arising in the mucosa of the head and neck is an infrequently encountered lesion. Approximately 15 percent of all malignant melanomas of the body occur in the head and neck, and of these only about one fifth arise in the mucosa. If one does not consider melanoma of the eye, melanoma of the upper respiratory tract and nasopharynx makes up only 1.8 percent of the body total, with ocular melanoma comprising nearly 80 percent of the noncutaneous melanomas (Scotto et al.).

On an annual age-adjusted incidence of nonskin melanoma, there appears to be one sixth the rate of cutaneous melanoma (0.7 to 100,000 population). For both skin and nonskin melanoma, the risk among whites is six times greater than among blacks.

Sex, Age, and Incidence. Sex distribution for mucosal melanomas shows a male predominance in nearly all series. The majority of patients are in their sixth and seventh decades of life when the diagnosis is made. Children are not immune, with several cases being recorded in young children.

Since melanocytes are present in the normal mucosa of the upper airway, malignant melanoma can occur at any location in this tract (Zak and Lawson; Busuttil). It is of interest that while melanocytes are present in the adult in the nasal mucosa, they are uniformly absent in fetal and neonatal mucosal material (Zak and Lawson). Conversely, melanocytes are observed in the masseter and temporalis muscles of all human fetuses and neonates, but are absent in adults. In the adult larynx (with the Masson-Fontana silver procedure for melanin) the scattered foci of melanocytes appear as dendritic cells situated in the basal layer of the squamous epithelial mucosal tissue (Goldman et al.).

Similar cells are found in the respiratory epithelium and stroma of the nasal septum, inferior and middle turbinates, and very likely in the paranasal sinuses. Rare junctional activity of these cells may occur.

Sinonasal Tract. Review of several major series indicates the primary sites of origin in the nose and paranasal sinuses are the nasal septum, lateral wall, and middle and inferior turbinates, corresponding to the distribution of melanocytes. Of the paranasal sinuses, the maxillary antrum exceeds the other sinuses by a 6 to 1 ratio. The nasopharynx is not a common primary site for melanoma. Melanomas rarely occur in the olfactory area of the superior nasal recess where pigmentation is normally quite abundant.

Clinical. Aside from an obstructive nasal mass, epistaxis, pain, and swelling of the tissues of the face are common complaints.

Gross. The gross presentation of these mucosal melanomas varies. Most of the lesions are polypoid tumors that are either pigmented or flesh colored. The latter simulate nasal polyps. In some patients, the entire nasal cavity may be filled by the neoplastic mass. Melanomas not presenting as polypoid tumors are quite often friable and hemorrhagic masses of varying color. The tumors may vary in size from 1.0 cm to an extensive tumor filling the nose and adjacent sinuses.

Microscopic. Cytologically, invasive melanomas of the upper airway (noncutaneous type) can be divided into three subgroups: polygonal or round cell ("carcinoma-like"); spindle cell; and mixed cell population (figs. 264-266). The spindle cell form is usually the most heavily pigmented and may appear "sarcomatous." The polygonal cell type is the most frequent and the mixed cell type the least frequent. The mitotic index of all forms of melanoma is high, with at least one mitotic figure per high power field. Junctional activity in the adjacent mucosa may be seen.

An unusual variant, balloon cell melanoma, may be mistaken for metastatic renal cell carcinoma or primary clear cell carcinoma.

Even though the lesion may be pale grossly, some melanin can be found if searched for and is present in over 90 percent of the neoplasms. Six of 56 mucosal melanomas from the Mayo clinic series were considered amelanotic (Freedman et al.).

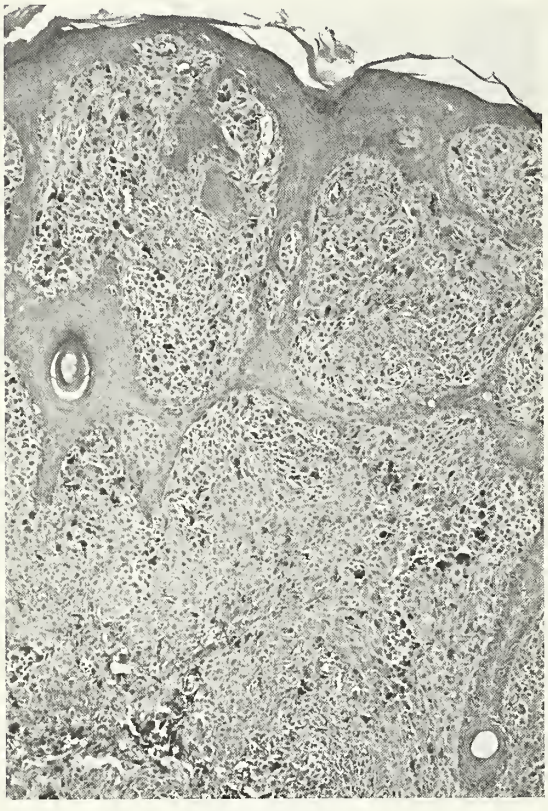

Figure 264
MELANOMA
A biopsy of an epithelioid malignant melanoma of the nasal cavity, with an overlying squamous metaplasia forming the surface and an anaplastic pigmented neoplasm infiltrating the soft tissue. X63.

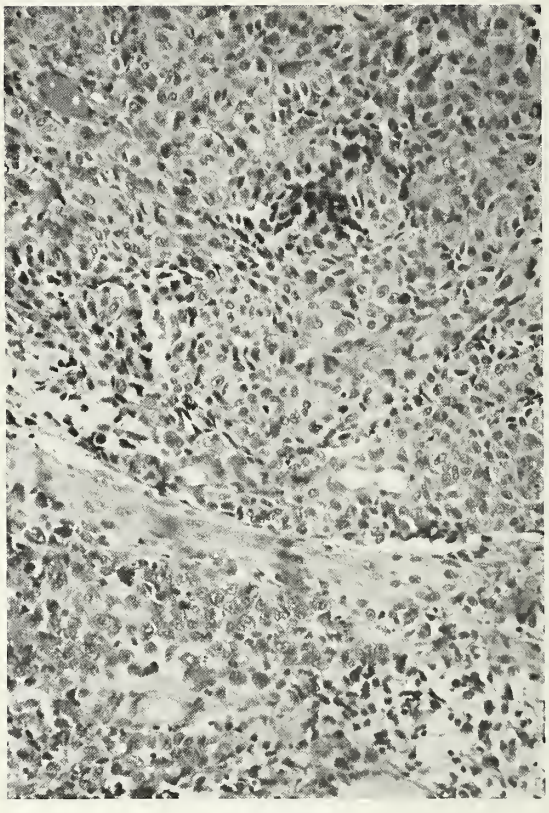

Figure 265
MELANOMA
An epithelioid type malignant melanoma of the nasal septum emphasizes the pleomorphic, anaplastic, neoplastic cell forming the invasive tumor. X160.

Confirmation of malignant melanoma may require special staining reactions or, rarely, electron microscopy. Pigment may be presumed to be melanin if it presents a positive reaction with the Fontana stain, does not form Prussian blue after the application of ferrocyanide, and is bleached with potassium permanganate solution.

Natural History and Prognosis. The mean survival time is shorter in mucosal than in cutaneous malignant melanomas. Holdcraft and Gallagher found that the five-year survival rate for malignant melanomas of the nasal and paranasal sinus mucosa was 11 percent (24 of a total of 226 patients). Only one patient survived for 10 years, and the five-year survival rate varied from 6 to 17 percent in cases of nasal and paranasal melanoma. This data contrasts with that of Freedman and associates, who report a 46 percent survival for three years and a 30.9 percent at five years, based on actuarial methods. Harrison records a 46 percent survival with freedom from disease at three years. His survival statistics were reduced to 28 percent at five years.

There is no constant correlation between survival and prognosis and size, location, pigmentation, and histologic appearance of the tumor. In that respect, patients with mucosal

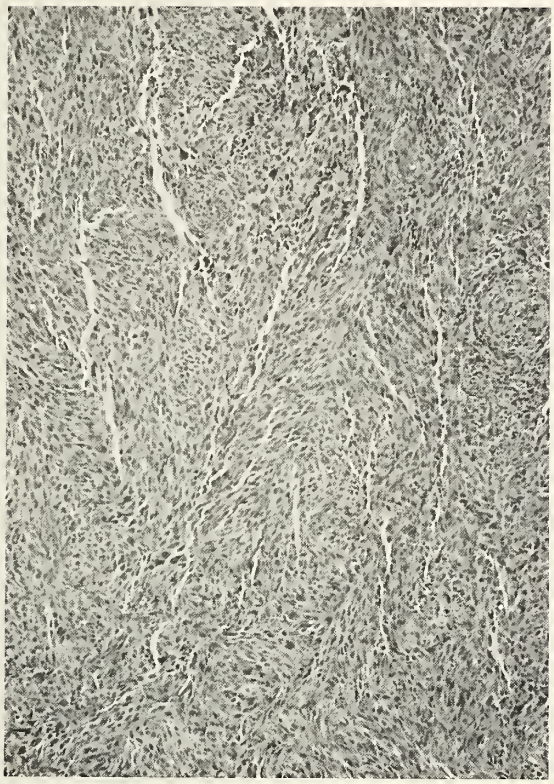

Figure 266
MELANOMA
This spindle cell malignant melanoma of the lateral nasal wall emphasizes the spindle cell morphology which suggests, at this magnification, a fibrosarcoma. X63.

malignant melanomas often have a very short survival, even though the primary lesion is small and the surgical procedure extensive. Local recurrences, as well as metastases to regional lymph nodes, however, do not preclude a prolonged quiescent period. Eneroth and Lundberg and Freedman and associates clearly indicate a continuing risk of death from melanoma, no matter how long after treatment the patient lives.

Metastases. The incidence of regional lymph node metastases from melanoma of the airway mucosa is relatively low compared to squamous cell carcinoma of the anatomic area, being less than 20 percent. Melanomas of the oral cavity have a higher incidence of metastases than those occurring either in the sinonasal or pharyngeal cavities.

Regional spread is to the orbit, infratemporal space, parotid gland, and the intracranial cavity. In the nasal cavity and paranasal sinuses, there is nearly a 50 percent incidence of local recurrence. Treatment failures are due for the most part to uncontrolled local disease or distant metastases. The latter occurs in approximately 20 percent of patients.

Larynx. Primary melanomas of the larynx are even more unusual than those in the superior airway. They have been reported from the supraglottis, epiglottis, and subglottis. By 1970, 15 examples of melanoma in the larynx had been recorded in the literature (Shanon et al.). One-third of these were metastatic to the larynx and ranks the melanoma with renal cell carcinoma as the most frequent metastatic neoplasm to larynx from remote primaries. Over a 40-year period, the AFIP-OTR contained only two cases of probable primary melanoma of the larynx.

HETEROTOPIC BRAIN TISSUE

SYNONYMS AND RELATED TERMS: Glioma; nasal glial heterotopia.

MENINGOENCEPHALOCELE

SYNONYMS AND RELATED TERMS: Encephalocele; meningocele.

Definition. These nonneoplastic tumors are extracranial neural tissues (with or without their mesodermal coverings). Most of the recorded examples have been localized in and around the nose and are seen most frequently as an encephalocele. The encephalocele retains a communication with the subarachnoid space. Other forms manifest no demonstrable connection to the

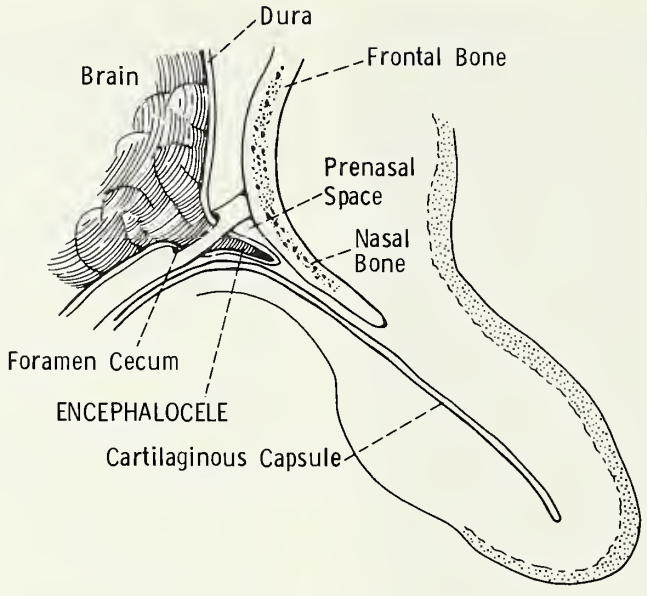

Figure 267
ENCEPHALOCELE
A sagittal section of the nose: encephalocele development. (Fig. 2 from Katz, A. and Lewis, J.S. Nasal gliomas. Arch. Otolaryngol. 94:351-355, 1971.)

cranial vault and are, in effect, an enclavement of brain tissue. The term "glioma" has been applied to both forms, and especially to the latter. The neoplastic connotation is inaccurate and we know of no example of a true glioma having arisen in these ectopic foci.

Pathogenesis. The origin of the encephalocele has been suggested by two theories: (1) from an arrested closure of the coverings of the brain through which neural tissue and meninges herniate; and (2) from an initial overgrowth of the neural tube, preventing a closure of the cranial covering (fig. 267). The heterotopic brain tissue with no demonstrable connection to the cranial vault may represent a misplacement of embryonic neural tube as it separates from the embryonic outer surface (figure 268).

The majority of patients (which is estimated as 1 in 4000 births) present with signs and symptoms during the first year of life with relative peaks of occurrence between 5 and 10 years of age (Karma et al.; Katz and Lewis). The sex incidence is nearly equal and there is no familial predisposition. A presentation during later life may be due to a failure to recognize a subclinical lesion in childhood or because of trauma.

Sites of Tumor. Three anatomic categories of encephalocele brain tissue exist. Seventy-five percent of cases are occipital, 15 percent are sincipital and situated above the dorsum of the nose, orbits, and forehead, and 10 percent are basal, presenting as a herniation into the superior meatus of the nasal cavity, epipharynx, and sphenomaxillary fossa. The occipital and sincipital forms may be visible

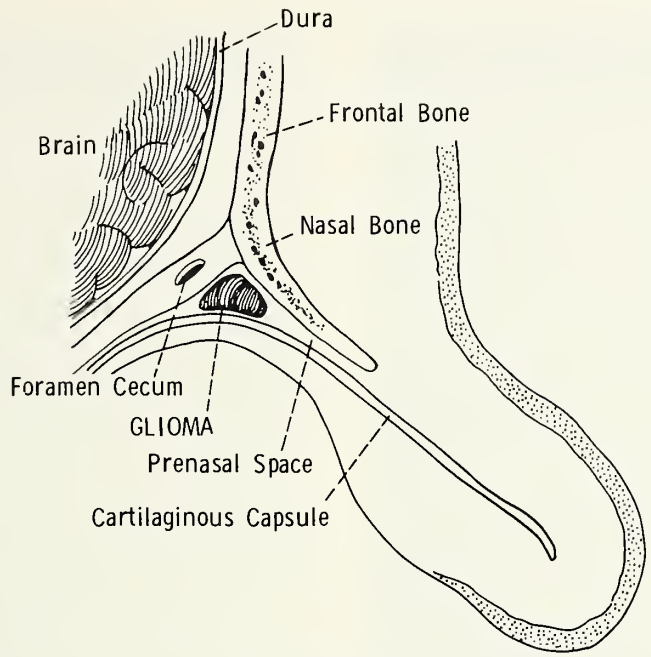

Figure 268
ENCEPHALOCELE
A sagittal section of the nose: glioma (ectopic central nervous system) development. (Fig. 3 from Katz, A. and Lewis, J.S. Nasal gliomas. Arch. Otolaryngol 94:351-355, 1971.)

externally. Basal forms have an internal presentation into the nasal pharyngeal spaces and, rarely, in the palate. Occipital encephaloceles are the most common type in Western Europe, while anterior encephaloceles are more frequent in eastern countries (Ramachandra and Phelps). Table 24 presents an anatomic subdivision of the basal and sincipital forms.

Clinical. Basal herniation (encephaloceles) do not produce a tumor visible in the face, but present in the nasal or nasopharyngeal cavities, or even in the mouth or posterior portion of the orbit or the sphenomaxillary fossa. A sphenopharyngeal basal encephalocele is the most common and clinically important by causing an obstruction and deformity of the airway and an ever-present threat of cerebral fluid rhinorrhea or meningitis.

Sincipital herniations may produce a tumor visible externally in the midline at the roof of the nose, at the junction of the body and cartilaginous portions of the nose, or near the inner canthus. These tumors present on either side of the bridge of the nose. The nasal roof and dorsum may be broadened, with a tendency toward wide-set eyes. The extranasal tumors are smooth, firm, elastic, and noncompressible. They are faint red or blue and do not increase in size with straining.

Intranasal presentation is readily mistaken for a nasal polyp, although the tumor is more dense, more glistening, and less translucent than the usual nasal polyp. Frequently a cause of nasal obstruction, they may displace the septum, nasal cartilages, or bone. The tumors appear attached by a stalk high within the nasal vault, from the middle turbinate or

Table 24

ANATOMIC VARIATIONS OF BASAL AND SINCIPITAL ENCEPHALOCELE

BASAL	
Transethmoidal:	Protrusion through a defect in the cribriform plate into the superior meatus
Sphenoethmoidal:	Protrusion into the epipharynx through a defect between the posterior ethmoid cells and the sphenoid
Transphenoidal:	Protrusion through a patent craniopharyngeal canal into the epipharynx
Sphenomaxillary:	Protrusion through the supraorbital fissure, through the infraorbital tissues and into the sphenomaxillary fossa; appears as a mass on the medial side of the mandibular ramus
SINCIPITAL	
Nasofrontal:	Protrusion between the nasal and frontal bones
Nasoethmoidal:	Protrusion through foramen cecum, separated from nasal interior by the ethmoid process
Naso-orbital:	Protrusion through the medial wall of the orbit; involving frontal, ethmoid, and lacrimal bones

the lateral wall of the nasal fossa. Adult onset lesions favor the latter locations (Enfors and Herngren). In the nasal adult encephalocele, a history should investigate the possibility of previous trauma or surgery in the anatomic area.

If intranasal and extranasal components are present (10 percent of cases), there is a communication between the two parts, usually through a defect in the nasal bone or at the lateral margin of the nasal bone.

Care must be exercised to differentiate the encephaloceles connecting directly with the subarachnoid or ventricular spaces from those ectopias in which the pedicle is broken, absorbed, or vestigial, forming the true nasal glial heterotopia of the so-called glioma (fig. 269).

Before any biopsy procedure is attempted in the case of an unexplained mass in the upper nasal cavity area or the base of the external nose, the clinical work-up should certainly include central nervous system studies, specifically CAT scans.

The growth of the tumors is usually slow and, in general, in accordance with the general growth of the host. In the encephalocele, spontaneous cerebrospinal fluid rhinorrhea may occur, but this is generally a complication of "polypectomy" or biopsy.

Gross. The tumors are generally of a firm consistency and are rarely recognized as brain, grossly. In the nasal cavity, the tumors are usually less than 1.5 cm and are firm, smooth, pink-white masses within a pseudocapsule. The extranasal tumors generally appear as solid, usually subcutaneous lesions astride or on either side of the midline through the base of the nose.

Microscopic. Most of the extracranial protrusions contain both glial and meningeal tissue (meningoencephalocele); some contain

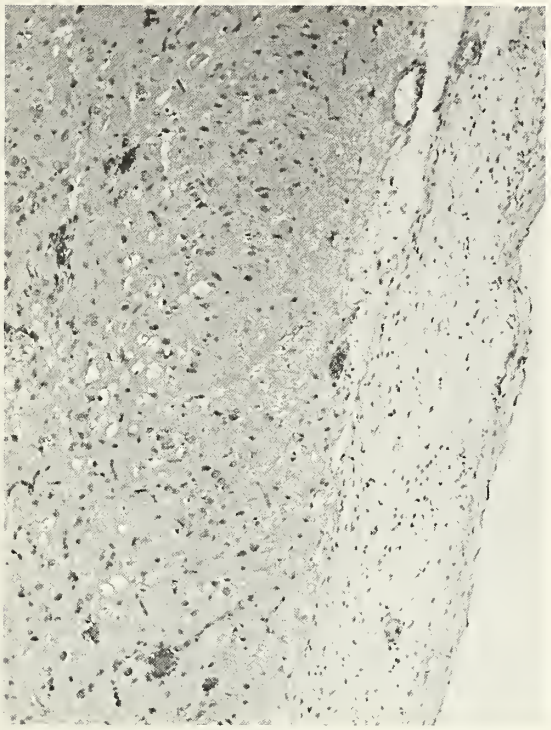

Figure 269
MENINGOENCEPHALOCELE
A portion of a meningoencephalocele presenting in the roof of the nasal cavity with a fibrous capsule (probably the leptomeninges) and underlying central nervous system tissue. X63.

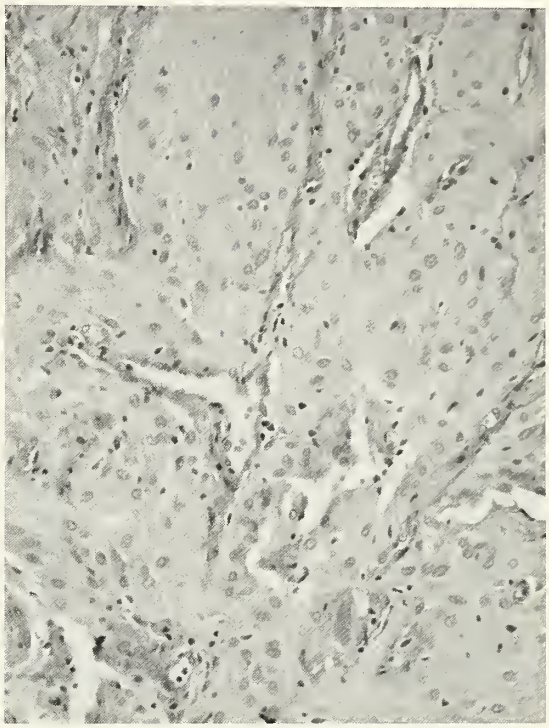

Figure 270
GLIOMA
A section of a heterotopic central nervous system (glioma) from the base of the external nose of a one year old boy, which reveals glial cells containing nerve-like tissue with prominent septate fibrous tissue throughout. X160.

a part of the ventricular system (meningoencephalocystocele).

The encephalocele generally will have the structure of the cerebral tissue of the anatomic area covered either by a fibrous mantle or by respiratory or olfactory epithelium.

In the heterotopic (glioma) mass, the glial tissue is subdivided by fibrous, vascularized septa which are continuous with the outer fibrous covering. A septate compartmentalization may be present. The glial cells are predominantly astrocytes. Gemistocytic forms are not unusual (fig. 270). Neuronal cells are usually sparse and Bodian silver impregnated preparations will demonstrate distinct, scattered axons.

Treatment and Natural History. The nasal heterotopias, which are separated from the cranial cavity, are not invasive, although approximately 10 percent have recurred following apparently incomplete excision. If there is no demonstrated central nervous system connection, then simple surgical removal will suffice; however, in the encephalocele, a craniotomy is required.

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TUMORS OF THE EAR

INTRODUCTION

There is no tumor entity that can be considered entirely unique to the human ear, but there are those which have a predilection for that organ. Other tumors, though more common in other parts of the body, pose special clinical and pathologic diagnostic problems in the temporal bone. Table 25 presents the diagnosis of neoplasms of the temporal bone area contributed to the AFIP-OTR during the years 1940 through 1975. This table affords a general classification as well as the frequency of neoplastic entities encountered in the temporal bone area. Tumor-like lesions, which compose a relatively large percentage of temporal bone pathology, even though not included in Table 25, will also be discussed in this section.

ANATOMY

The ear is divided into the external, middle, and inner segments (fig. 271).

External Ear. The external ear consists of the auricle or pinna, and the less visible external acoustic meatus or auditory canal. The external auditory canal is divided into a cartilaginous or outer portion and the osseous or inner portion. In the adult, the cartilaginous portion accounts for one-third of the canal, while the inner two thirds comprises the osseous portion. At birth, the tympanic ring of bone which eventually develops into the osseous portion of the auditory is immature and evolves into a prominent bony sleeve during childhood. In the superior and

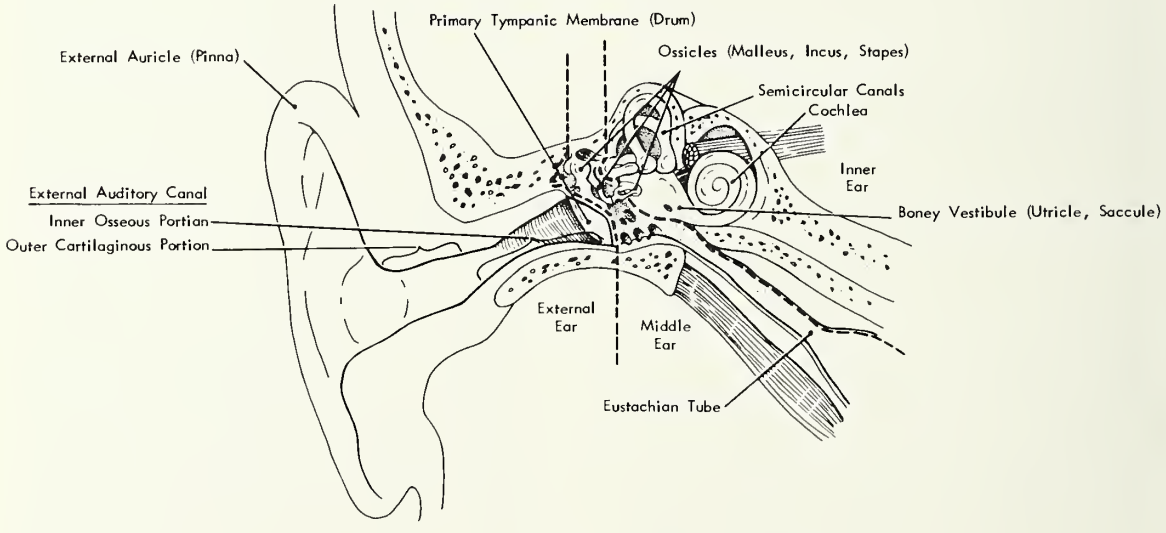

Figure 271
ANATOMY
The external (auricle, external auditory canal), middle (eustachian tube, mesotympanum, epitympanum, mastoid), and inner (membranous, osseous labyrinth) ear are the three main divisions separated by the dotted lines in this drawing.

posterior parts of the cartilaginous portion, there is a defect which is replaced by firm connective tissue that is continuous internally with the periosteum of the bony canal. These defects or fissures render the cartilaginous canal very pliable and flexible. The cartilage of the auricle is in continuity with that encompassing the outer portion of the canal. The inner portion of the canal is limited medially by the drum or primary tympanic membrane, a thin epithelial and fibrous membranous structure which forms also a portion of the lateral anatomic boundary of the middle ear.

Middle Ear. The middle ear contains the auditory ossicles (malleus, incus, and stapes) and this anatomic space is referred to collectively as the middle ear cleft, which includes the eustachian tube, middle ear proper with the epitympanic space (attic), and the mastoid cavity and its contiguous pneumatic spaces. The mastoid, pneumatic or air spaces, are not developed in the newborn, but develop later. A small percentage of adult humans reveal unpneumatized or sclerotic mastoids due possibly to congenital abnormalities or inflammatory influence early in the neonatal period. Additional pneumatized air cells of variable distribution and amount may arise throughout the temporal bone originating from the mastoid antrum and other areas of the middle ear cleft, including the eustachian tube.

Inner Ear. The inner ear comprises the medial portion of the temporal bone adjacent to the cranial cavity and contains the membranous organs of hearing and equilibrium, the cochlea, and the vestibular labyrinth. These structures are well protected by an osseous layer composed of special and normal bone structures referred to as the bony labyrinth. The neural structures supplying the inner ear (eighth cranial nerve) as well as the facial nerve (seventh cranial nerve) enter the inner ear through a prominent cylindrical bony tube, the internal auditory canal.

EMBRYOLOGY

The external auditory canal develops from the first branchial groove or cleft and is considered a normal remnant of this branchial groove (fig. 272). It meets the first branchial pouch that forms the middle ear at the precursor of the tympanic membrane (eardrum). The external auricle (pinna) forms around the external portion of the first branchial groove from tissue contributions (hillocks, tubercles) of the first and second branchial arches. The middle ear spaces are a development of the invagination of the first branchial pouch (pharyngeal tympanic tube) from the primitive pharynx (fig. 273). The ossicles form from the first and second branchial arch tissue (Meckel's and Reichert's cartilages) (fig. 274). The inner ear structures develop from the otocyst which migrates into this position (fig. 273) following its differentiation from surface ectoderm. The osseous labyrinth and its soft tissue elements are mesodermal contributions (Dayal et al.).

HISTOLOGY

The external auricle (pinna) differs little from the histology of the general skin surface. There is a thin, slightly keratinizing, stratified squamous epithelial surface with the dermic and subcutaneous tissue containing variable distributed small hair follicles, sebaceous glands, and eccrine sweat glands. The subcutaneous tissue of the auricle is of a fibroareolar type, being somewhat more

Table 25

NEOPLASMS OF EXTERNAL AND MIDDLE EAR AND TEMPORAL BONE
AFIP Otolaryngic Tumor Registry (1940-1975)

Diagnosis	External Auricle	External Auditory Canal	External Ear-NFC*	Middle Ear	Temporal Bone-NFC*
Squamous papilloma	1	32	25	—	—
Keratoacanthoma	—	—	11	—	—
Basal cell carcinoma	13	13	368	—	—
Bowen's disease — carcinoma in situ	12	—	—	—	—
Squamous cell carcinoma	30	58	315	25	—
Adenoid squamous carcinoma	—	—	34	—	—
Nevi, pigmented	—	5	111	1	—
Melanoma	2	—	27	2	—
Pilomatrixoma	—	—	4	—	—
Adenoma	—	25	—	45	—
Mixed tumor	—	9	—	—	—
Syringocystadenoma papilliferum	—	4	—	—	—
Sebaceous adenoma	1	1	—	—	—
Sebaceous adenocarcinoma	—	2	—	—	—
Adenocarcinoma	—	18	—	2	—
Adenoid cystic carcinoma	—	19	—	5	—
Carcinoma (NFC)	—	3	—	2	9
Fibroma	1	1	6	2	—
Fibroxanthomatous tumors (benign)	—	10	—	—	—
Fibroxanthomatous tumors (malignant)	—	—	2	—	—
Aggressive fibromatosis	—	2	—	—	—
Fibrosarcoma	2	1	1	—	—
Fibromyxoma (sarcoma?)	—	3	—	2	—
Dermatofibroma	2	—	6	—	—
Kaposi's sarcoma	1	1	—	—	—
Lymphangioma	—	1	—	1	2
Rhabdomyosarcoma	1	10	8	8	—
Sarcoma (NFC)	—	1	1	2	2
Osteoma	—	44	—	1	—
Osteosarcoma	—	—	—	—	2
Chondroma	2	1	—	1	6
Chondrosarcoma	—	—	—	—	4
Ossifying fibroma	—	1	—	11	—
Fibrous dysplasia	—	—	—	1	—
Giant cell tumor	—	—	—	—	3
Histiocytosis "X"	—	2	—	10	—

*NFC = Not further classified

Table 25 (Continued)

Diagnosis	External Auricle	External Auditory Canal	External Ear-NFC*	Middle Ear	Temporal Bone-NFC*
Glioma (heterotropic)	—	—	—	5	—
Neurilemoma	—	3	—	3	200+
Neurofibroma	—	8	—	—	4
Meningioma	—	1	—	17	—
Paraganglioma (glomus jugulare)	—	14	—	76	—
Lymphoma (non-Hodgkin's)	1	—	—	2	1
Metastatic neoplasms					
Squamous cell carcinoma	—	2	—	3	1
Adenocarcinoma	—	3	—	20	1
Sarcoma	—	1	—	—	—
Malignancy (NFC)	—	5	—	6	2
Dermoid	—	—	—	—	10
Hamartoma	—	2	—	1	2
Choriostoma	—	—	—	2	—

Additional neoplasms, only one case recorded:
Seborrheic keratosis; Paget's disease of skin; Verrucous carcinoma; Spindle cell carcinoma; Blue nevus; Juvenile melanoma; Mucoepidermoid carcinoma; Nodular fasciitis; Dermatofibrosarcoma protuberans; Leiomyoma; Leiomyosarcoma; Osteoblastoma; Neuroblastoma; Granular cell tumor; Angiosarcoma.

*NFC = Not further classified

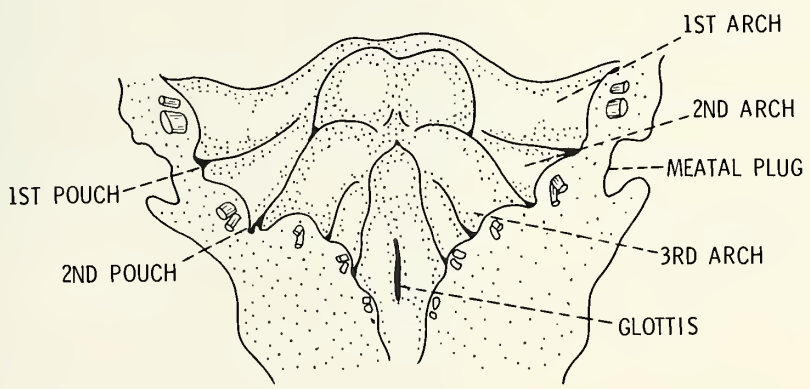

Figure 272
EMBRYOLOGY
This anterior view of the foregut emphasizes the first three branchial arches and the arrangement of projecting pouches arising from the inner surface of the arches, as well as the first branchial cleft (meatal plug) indenting on the outer surface to form the external canal. (Fig. 36 from Davies, J. Embryology of the Head and Neck in Relation to the Practice of Otolaryngology. Washington, DC: American Academy of Otolaryngology, 1957.).

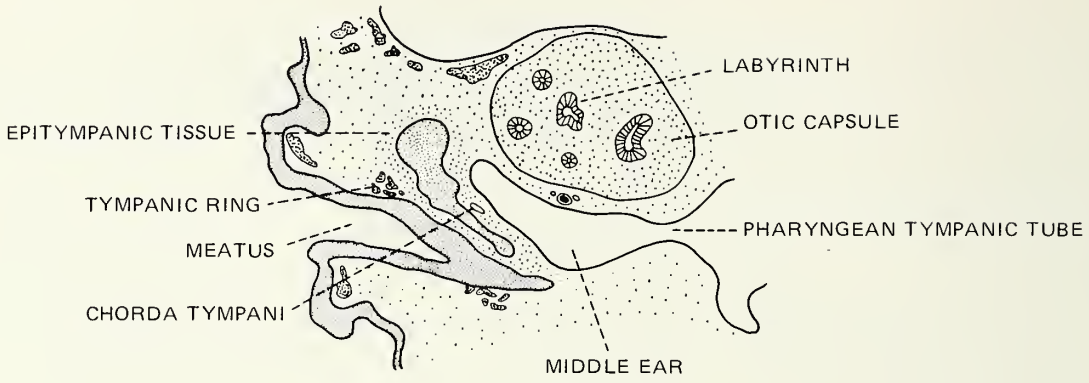

Figure 273
EMBRYOLOGY
This drawing further elaborates the arrangement of the first external cleft forming the external auditory canal (meatus) and first branchial pouch (pharyngeal tympanic tube) forming the early middle ear space. The relationship of the inner (labyrinth and otic capsule) and the mesenchymal and neuroectodermal structures (ossicle, tympanic ring, chorda tympani) are noted. (Fig. 39 from Davies, J. Embryology of the Head and Neck in Relation to the Practice of Otolaryngology. Washington, DC: American Academy of Otolaryngology, 1957.)

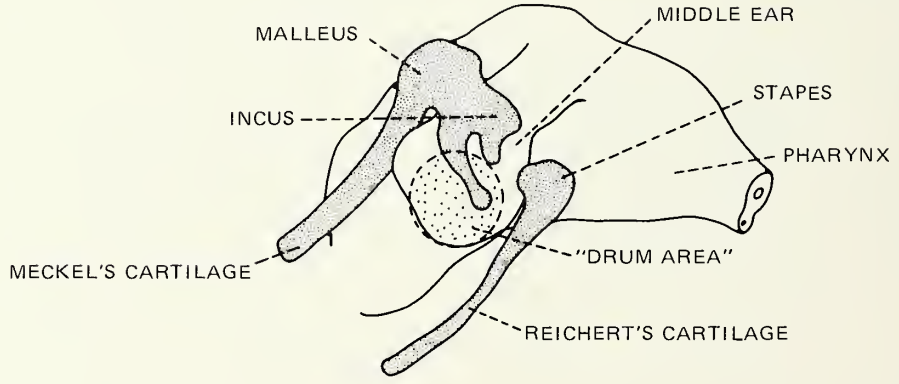

Figure 274
EMBRYOLOGY
The ossicles form from the proximal portion of Meckel's and Reichert's cartilage, which are cartilaginous bars arising in the first and second branchial arches respectively. The more distal portions of the cartilages regress to essentially fibrous bands and ligaments. (Fig. 37 from Davies, J. Embryology of the Head and Neck in Relation to the Practice of Otolaryngology. Washington, DC: American Academy of Otolaryngology, 1957.)

areolar and loosely textured on the posteromedial surface when compared with the anterolateral area (fig. 275). Adult type fatty tissue comprises the subcutaneous tissue of the lobe. Structural support for the auricle is furnished by a central subcutaneous elastic cartilaginous plate in continuity with the cartilage tube contained in the outer portion of the external auditory canal. The external auditory canal is lined also by keratinizing stratified squamous epithelium throughout to include the external surface of the tympanic membrane. In the inner half of the canal, the epidermis is thin and without rete pegs. Adnexal structures are concentrated in the outer third of the canal with relatively few being scattered in the superior quadrant of the inner portion. Hair follicles, sebaceous glands, and apocrine glands (ceruminal glands) form the adnexa, the last named replacing the eccrine sweat glands found on the pinna and skin surface (fig. 276). The ceruminal glands deserve special attention because of their unique histology and they are usually the origin of primary adenomatous neoplasms of the external canal. They are arranged into grapelike clusters in the deeper dermis and subcutaneous tissue. The secretory elements reveal a distinctive luminal surface cell layer of cuboidal to columnar epithelium with eosinophilic cytoplasm and frequent secretory droplets on the luminal surface (fig. 277). These lining cells have an atrophic appearance following secretion (fig. 278). Golden brown pigment granules are often seen within the cytoplasm. These

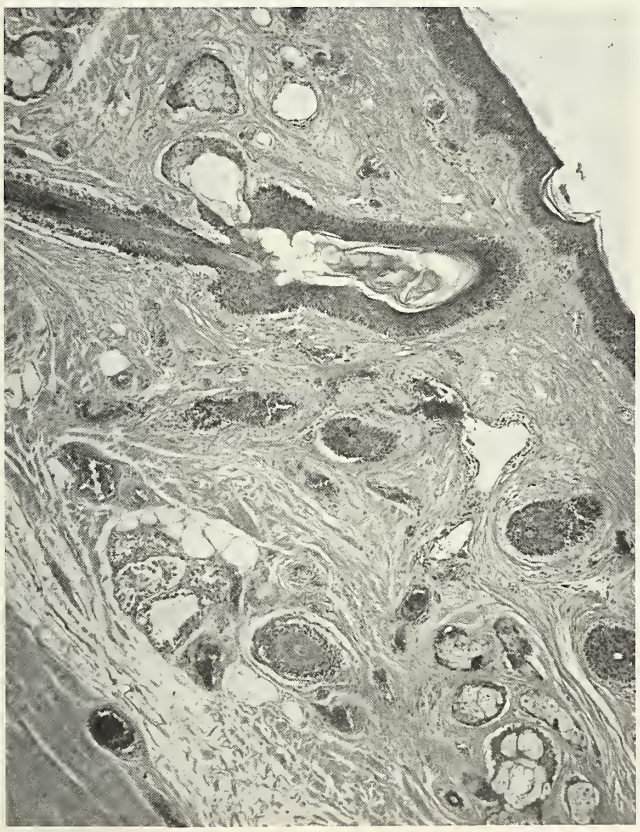

Figure 275
EXTERNAL AURICLE
A section of the external auricle emphasizes the adnexa in the dermis and subcutaneous tissue. X63.

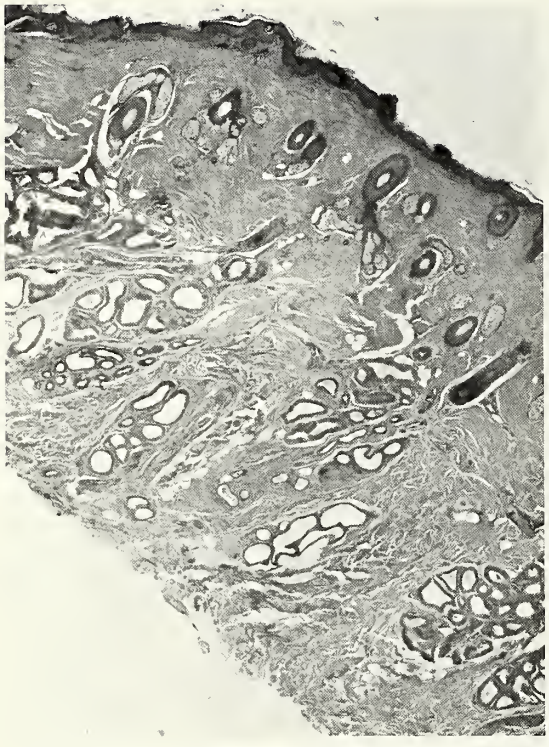

Figure 276
EXTERNAL AUDITORY CANAL
The surface of the outer third of the external auditory canal consists of keratinizing squamous cell epidermis with hair follicles and sebaceous glands in the dermis and abundant apocrine ceruminal glands replacing the exocrine sweat glands that are present in the subcutaneous tissue in the external auricle. X25.

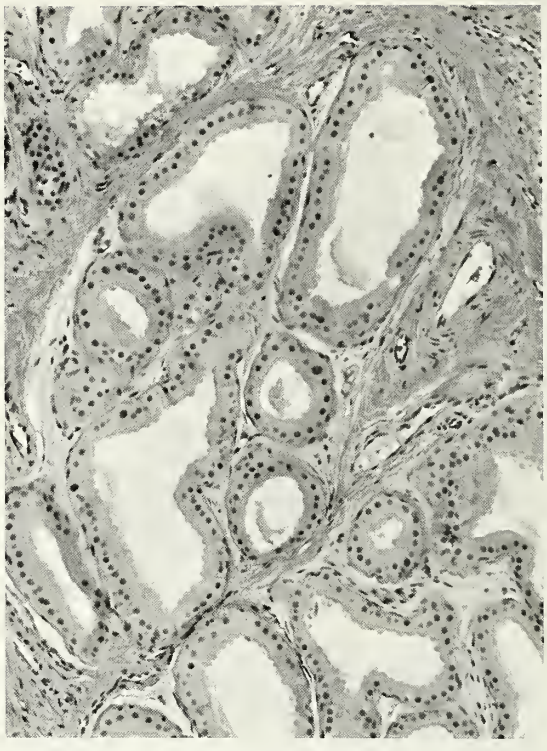

Figure 277
CERUMINAL GLANDS
Apocrine ceruminal glands consist of tall secretory epithelium with secretory droplets on the lumenal surface. An occasional myoepithelial cell will be seen at the base of the secretory cells. X125.

granules may be diastase resistant/PAS positive, appear to consistently stain with Sudan black and toluidine blue, and also occasionally by the Ziehl-Nielssen acid fast method. Some may also give a positive Prussian blue reaction. The cytoplasm of the surface secretory cell is also diastase resistant PAS positive. There is an outer layer of elongated myoepithelial cells in intimate contact with the secretory cells. A basement membrane separates both from surrounding connective tissue elements. The ducts leading to the skin surface consist of two rows of small, cuboidal, dark staining cells. Electron microscopic study (Wetli et al.) supports an apocrine nature of the inner secretory cell layer, but more recent investigation by Main and Lim suggests also an eccrine function for the secretory cell. The drum or primary tympanic membrane consists of fibrous connective tissue covered externally by a thin layer of keratinizing stratified squamous epithelium, and on the inner surface by a single layer of cuboidal cells. The excellent monographs by Lim of the makeup of this structure is recommended to the interested reader (fig. 279).

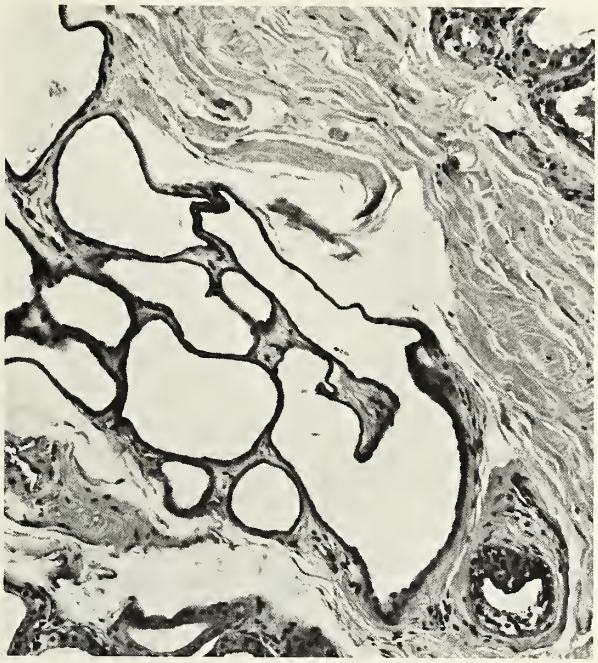

Figure 278
CERUMINAL GLANDS
Apocrine ceruminal gland, following secretion, has a flattened nucleus and scanty cytoplasm in the remaining portions of the secretory cells. X25.

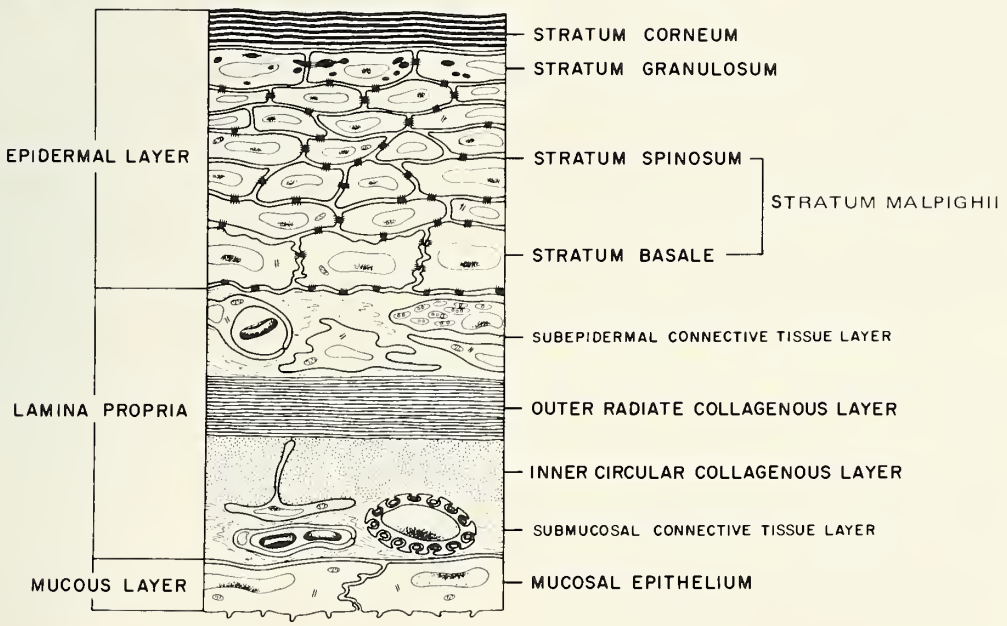

Figure 279
PRIMARY TYMPANIC MEMBRANE
A schematic microscopic view of a cross section of the pars tensa of the primary tympanic membrane (ear drum). The epidermal layer faces the external auditory canal. The pars flaccida (Shrapnell's membrane) portion of the drum consists of a similar histology makeup minus the outer and inner collagenous layer. (Fig. 1 from Lim, D.J. Tympanic membrane. Electron microscopic observation. Part I. Pars tensa. Part II. Pars flaccida. Acta Otolaryngol. 66:181-198; 515-532, 1968.)

Table 26

CLASSIFICATION OF TUMORS OF THE EXTERNAL EAR (AURICLE, EXTERNAL AUDITORY CANAL)

Tumor-like lesions
- Chondrodermatitis nodularis chronica helicis (Winkler's disease)
- Benign angiomatous nodules (subcutaneous angiolymphoid hyperplasia with eosinophilia, Kimura's disease)
- Keloid
- Malignant (necrotizing granulomatous) external otitis
- Accessory tragi (supernumerary auricle)
- Choristoma, hamartoma
- Inflammatory polyps

Cysts
- Idiopathic cystic chondromalacia (pseudocysts)
- Congenital cysts (first branchial cleft anomalies)
- Traumatic cysts
  - Epidermoid inclusion cyst
- Epidermal cyst
- Sebaceous (pilar) cyst
- Pilomatrixoma (calcifying epithelioma of Malherbe)

Benign neoplasms
- Squamous cell papilloma
  - Seborrheic keratosis (basal cell papilloma)
  - Sebaceous adenoma or papilloma
- Nevi
- Ceruminal gland adenoma
  - Mixed tumor of ceruminal gland origin
  - Syringocystadenoma papilliferum

Questionable malignant or premalignant epithelial neoplasms
- Keratoacanthoma
- Solar keratosis (senile keratosis, actinic keratosis)

Malignant neoplasms
- Ceruminal gland adenocarcinoma
  - Adenoid cystic carcinoma of ceruminal gland origin
- Basal cell carcinoma
- Squamous cell carcinoma
  - Adenoid squamous cell carcinoma
- Malignant melanoma

The middle ear spaces (middle ear proper, mastoid, and eustachian tube) are lined by a modified respiratory epithelium (Hentzer). It appears mainly as flattened single layered pavement type epithelium in the mastoid and the major portion of the middle ear (fig. 280) with a transition to a ciliated epithelium in the eustachian tube and its middle ear approaches. Middle ear epithelium may transform in any anatomic area to ciliated secretory epithelium as a result of inflammatory stimulation. The submucosal tissue is a thin layer of fibrous tissue containing inconspicuous vascular and peripheral neural structures. The inner ear structures are not described here because of the complexity of this anatomic area, and the infrequency of primary neoplasia in the inner ear area does not merit the complicated discussion that would be appropriate. However, one must be aware of the prominent occurrences of acoustic neuromas reported in the internal auditory canal.

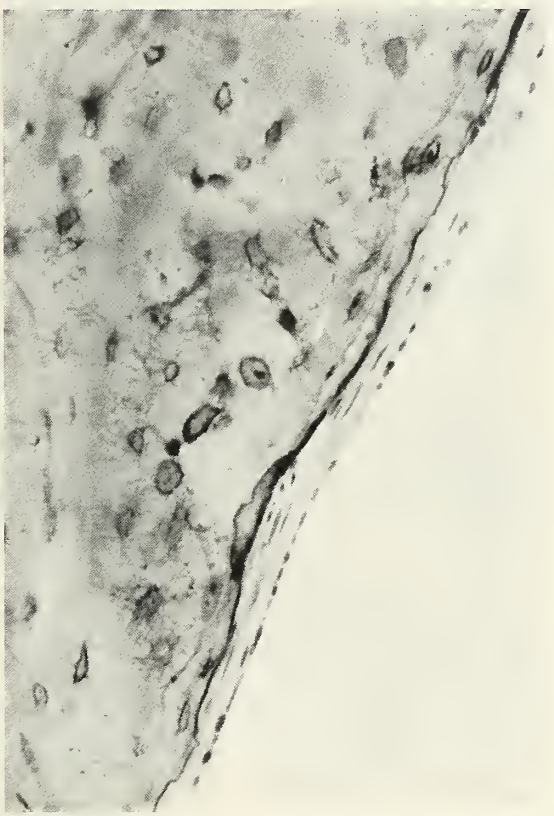

Figure 280
MIDDLE EAR
A microscopic view of the normal middle ear mucosa with a flattened, single layered, epithelium mucosal surface and narrow fibrous submucosal layer. X320.

In the following discussion, tumor-like lesions and neoplasms of the ear are organized into those that are primary in the external ear (auricle and external auditory canal) (Table 26); those of the middle ear (eustachian tube, mesotympanum, epitympanum, and mastoid cavity area); and the inner ear (including the internal auditory canal). Occasionally, where a pathologic entity originates in more than one anatomic area of the ear, it will be discussed under the region of its most common occurrence.

Of the 1789 neoplasms of the temporal bone ear listed in the AFIP-OTR (1940-1975) (Table 25), 72 percent arose from the external ear, 12 percent from the middle ear, and 16 percent from the inner ear, the latter being essentially acoustic nerve neurilemomas of the internal auditory canal. During this period, 31 patients with metastatic neoplasms to the ear from regional and distal sites are recorded.

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Hentzer, E. Ultrastructure of the middle ear mucosa. Ann. Otol. Rhinol. Laryngol. 85(Supp. 25):30-35, 1976.

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Main, T. and Lim, D. The human external auditory canal secretory system — an ultrastructural study. Laryngoscope 86:1164-1176, 1976.

Wetli, C.V., Pardo, V., Millard, M., and Gerston, K. Tumors of ceruminous glands. Cancer 29:1169-1178, 1972.

TUMOR-LIKE LESIONS OF THE EXTERNAL EAR

The terminology, tumor-like, refers to lesions that clinically or morphologically resemble neoplasms, but do not behave in a neoplastic manner. They are important because they can often be mistaken clinically and even pathologically with neoplasia and, in some cases, there is an ill defined borderline between neoplasm and some nonneoplastic lesions.

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS (WINKLER'S DISEASE)

This entity is a discrete, small nonneoplastic lesion involving usually the superior portion of the helix of the external auricle in late middle-aged or older patients; however, the lateral helical rim and antihelix may also be the primary site. In a recent review, Metzger and Goodman have reported a 30 percent incidence in females. The cause is undecided, with the lesion presenting spontaneously as a discrete oval nodule with a raised center, often containing a crust or scale. Clinically, it is often mistaken for a basal cell or squamous cell carcinoma or premalignant keratosis, but growth stops after it reaches a size of approximately 3 mm to 1.5 cm. Pain on manipulation is dramatic and a predominant symptom. Microscopically, the epidermis presents a marked acanthosis and pseudoepitheliomatous hyperplasia with varying degrees of hyperkeratosis and parakeratosis. The central epidermis may show erosion, exposing an inflammatory ulcerative base with findings of edema, fibrinoid necrosis, granulation tissue, and varying mixed inflammatory cell infiltrates. The perichondrium is usually involved by this inflammatory process, granulation tissue, or fibrinoid necrosis. The auricular cartilage in the immediate area of the lesion may show alterations (figs. 281, 282). Treatment has been complete surgical removal; however, reports of successful eradication by injection of intralesional glucosteroids would suggest a trial with this therapeutic modality. There is no premalignant connotation reported with this entity.

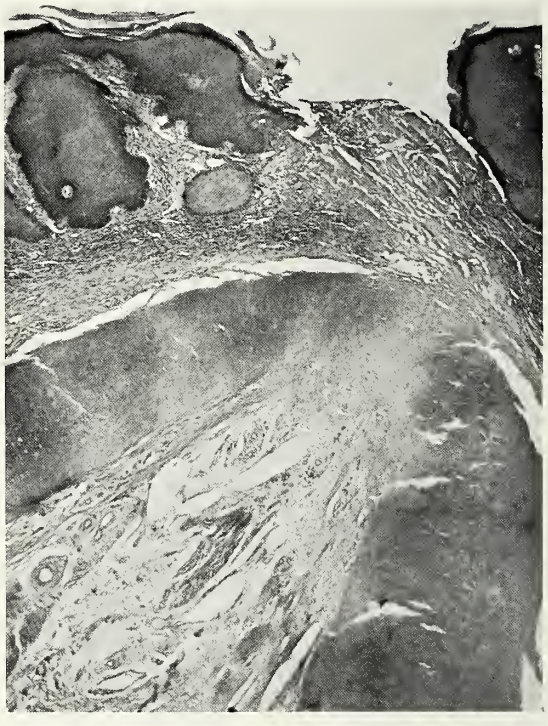

Figure 281
(Figures 281 and 282 are from the same patient)
CHONDRODERMATITIS NODULARIS CHRONICA HELICIS
Histology of chondrodermatitis nodularis chronica helicis emphasizes the surface ulceration and adjacent pseudoepitheliomatous hyperplasia of the epidermis. X25.

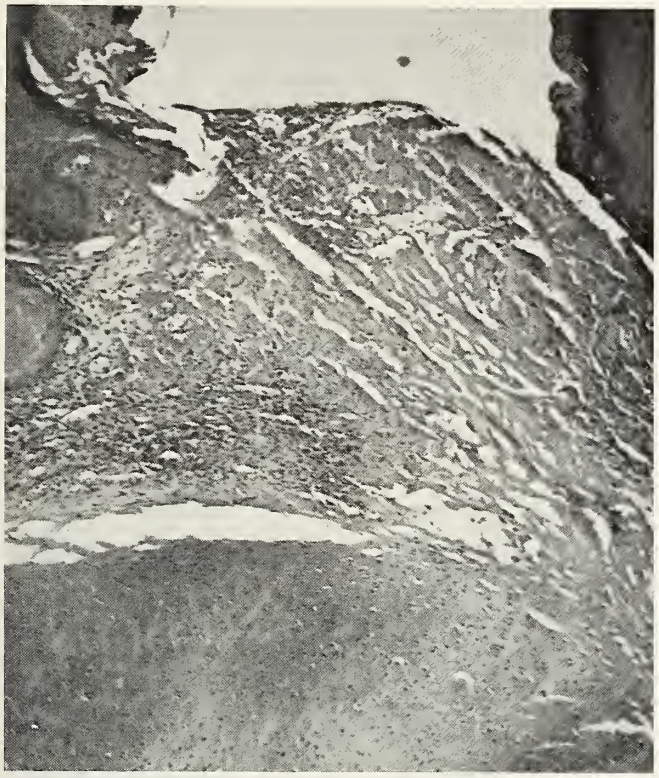

Figure 282
CHONDRODERMATITIS NODULARIS CHRONICA HELICIS
Note the involvement of the perichondrium and cartilage by granulation tissue at the bed of the ulcer, which accounts for the painful symptoms. X160.

BENIGN ANGIOMATOUS NODULES OF THE FACE AND SCALP

SYNONYMS AND RELATED TERMS: Atypical pyogenic granuloma; subcutaneous angiolymphoid hyperplasia with eosinophilia; papular angioplasia; Kimura's disease; inflammatory angioplasia.

This entity is a nodular vascular lesion of the dermis and subcutaneous tissue reported in single or multiple manifestations occurring at any surface skin site, particularly the scalp, but having predilection for the external auricle and auditory canal area (Mendonca; Thompson et al.).

The pathogenesis is undetermined and it is a self-limiting benign process, even though clinically and histologically it can be mistaken for an aggressive or malignant vascular neoplasm. Any age is susceptible, but occurrence is mainly in adults of young and middle age, with no sex predominance (Barnes et al.). Rosai and associates suggested this entity be included as part of the "histiocytoid hemangioma" group, which includes many vascular lesions of the skin, intravascular atypical vascular proliferations, and others.

Gross. The lesions are sessile or plaque-like, slow growing, skin colored to dull red or blue, occasionally with superficial bleeding and crusty scaling due to scratching by the patients because of the accompanying pruritus. Individual lesions vary from 2 mm to 1 cm, but may coalesce to a large plaque which can become obstructive if located in the external auditory canal.

Microscopic. The process may or may not be circumscribed and the lesions consist in part of a vascular component comprised of

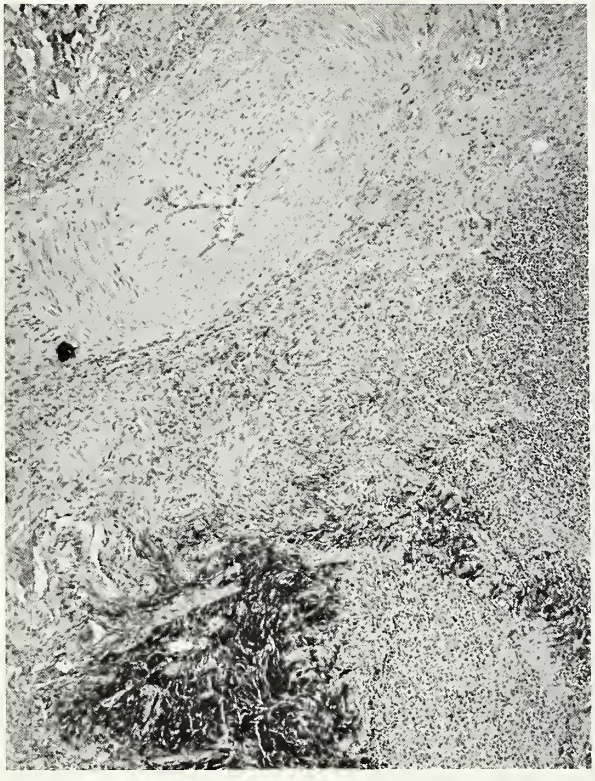

Figure 283
BENIGN ANGIOMATOUS NODULE
This microscopic view reveals the diffuse lymphoid inflammatory cell infiltration as well as the occasional larger vessel that can be involved. X63.

small, thick-walled vessels and capillaries lined by plump, sometimes multilayered, moderately atypical endothelial cells (figs. 283, 284). Occasionally, a large artery or vein with marked intimal fibrous proliferation will be part of the vascular component. In addition to the vascular element, there will usually be an inflammatory cell component, varying from diffuse benign lymphoid hyperplasia with germinal follicles to a varying mixture of eosinophils, mononuclear cells, and mast cells.

Treatment. Localized surgical removal, local desiccation, possibly by laser application, steroid injection, or systemic steroid application is recommended. Occasional recurrence is reported, however, and some lesions have been noted to atrophy without treatment.

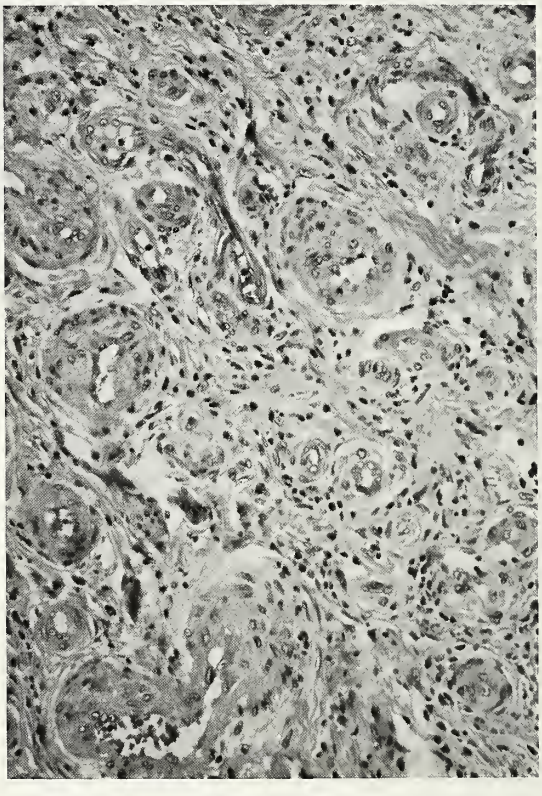

Figure 284
BENIGN ANGIOMATOUS NODULE
This benign angiomatous nodule shows the typical vascular component comprised of small, thick-walled vessels lined by plump, sometimes multilayered, moderately atypical endothelial appearing cells. X160.

KELOIDS AND POST TRAUMATIC SCARRING OF THE EXTERNAL EAR

A keloid is a post traumatic lesion occurring in a susceptible individual and, when seen involving the external auricle, is almost always the result of piercing the ear lobe for earring insertion. The black race is particularly afflicted. Lacerating trauma can also initiate keloid formation (fig. 285), but the so-called cauliflower ear is not related to keloid formation. (The post traumatic subperichondrial hemorrhage and fluid retention in the latter causes nutrient deficiency to the auricular cartilage, with the resultant necrosis and replacement by scar tissue. It may be hypertrophic, but not to the extent seen in the usual keloid formation). Microscopically, the overlying epidermis is unremarkable, but the dermis and subcutaneous tissue contains a collection of moderately demarcated bundles of multisized hyalinized collagenous fibers intermixed with fibroblasts. Adnexa are atrophic (fig. 286). Treatment by surgery alone may lead to recurrence, but postoperative small doses of irradiation or injection of the involved area by glucosteroids has been advocated to circumvent recurrence.

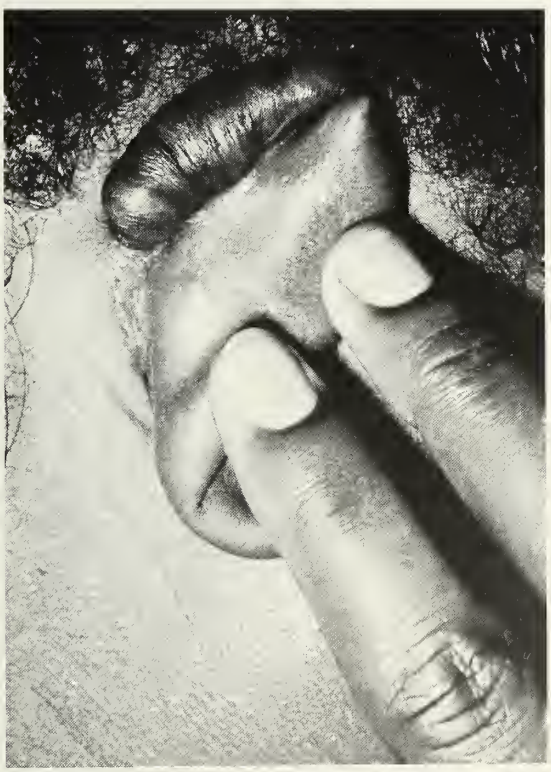

Figure 285
KELOID
This 18 year old black woman had worn glasses for four years, and for the past three months had noted this slow growing, right-sided, retroauricular tumor. She knew of no specific trauma, except for the irritation of the glasses resting on the ear.

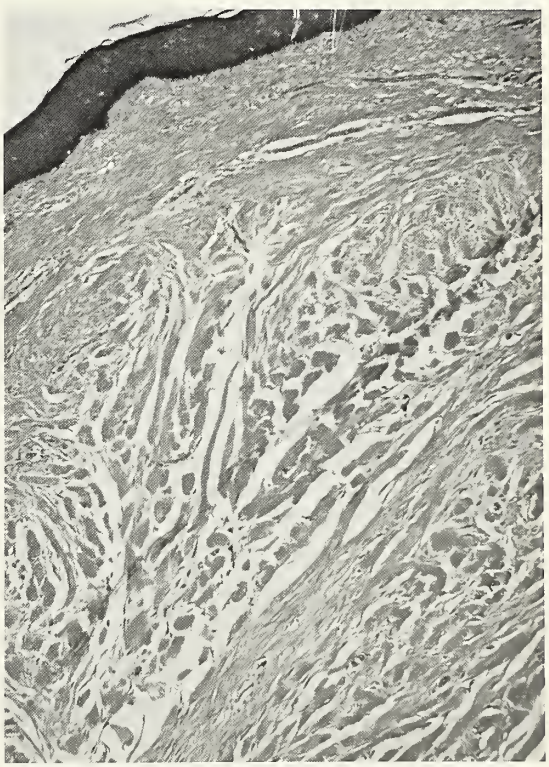

Figure 286
KELOID
The histology of a keloid consists of an unremarkable surface epidermis, but the dermis and subcutaneous tissue is occupied by moderately demarcated bundles of hyalinized collagenous fibers intermixed with fibroblasts. Adnexa are atrophic. X63.

MALIGNANT EXTERNAL OTITIS

Malignant external otitis (necrotizing granulomatous otitis) is a vicious form of external otitis said to be related to Pseudomonas aeruginosa infection and it afflicts mainly the elderly diabetic patient (fig. 287). Zaky and associates reported a mortality of 53 percent in a literature review of 34 cases; however, the prognosis for cure of this condition has steadily improved with early recognition and treatment (Neal and Gates). The severe external ear canal infection spreads through clefts in the external auditory canal to involve surrounding soft tissue, the bone, and middle ear cleft, with resultant involvement of the facial nerve and other cranial nerves and, possibly, eventually meningitis.

Microscopic. The microscopic finding is that of necrotizing inflammation involving elastic cartilage, bone, and soft tissue. The deep-seated necrosis seems incompatible with infection by Pseudomonas aeruginosa only, an organism which is aerobic and requires considerable amounts of oxygen for its growth. It seems likely that anaerobic organisms, such as Bacteroides, also play a part in the genesis of this disease. Treatment by medical management with newly developed antibiotics effective against the Pseudomonas organism is preferred (Neal and Gates); however, the more advanced and refractory infections may be cured with the addition of heroic surgery.

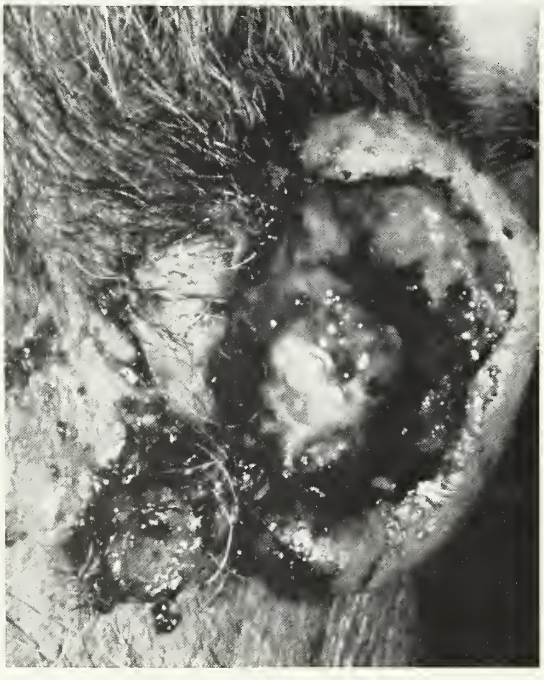

Figure 287
MALIGNANT EXTERNAL OTITIS
An elderly diabetic gentleman developed a draining external otitis which showed an aggressive tendency by destroying the ear drum. The organism cultured was of the Pseudomonas species. This is a rather severe, malignant, external otitis media.

ACCESSORY TRAGI

SYNONYMS AND RELATED TERMS: Accessory ear; supernumerary auricle

These are unilateral or bilateral sessile, pedunculated or acuminate papules or nodules appearing at birth and located on the skin surface anterior to the auricle in the pretragal area (fig. 288) (Brownstein et al.). They are soft or cartilaginous, skin-covered, and measure an average 5 mm in diameter and up to 1 cm in length.

Histology. The structure is that of the normal external auricle. They have been mistakenly diagnosed as papillomas and fibromas. The origin is apparently due to congenital malformation related to the second branchial arch system, since similar accessory structures are occasionally found on the skin or neck. Simple surgical removal is curative.

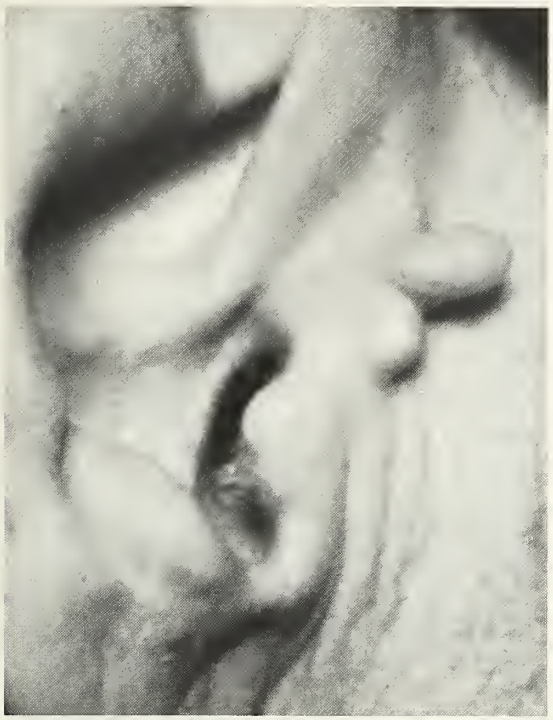

Figure 288
ACCESSORY TRAGI
This patient was a 32 year old woman who stated she had had bilateral nontender growths in the preauricular area ever since she could remember.

CHORISTOMA AND HAMARTOMA

Although ectopic tissue, particularly salivary gland, is not unusual in the middle ear or neck region, the AFIP-OTR (Table 25) does not contain a choristoma of the external ear. Braun and associates, however, reported a well documented case of bilateral ectopic salivary gland tissue within the external auditory canals. Kacker and Dasgupta described a benign external auricular tumor that was considered pathologically a hamartoma. Other than these two reports, the English medical literature does not support the occurrence of teratomas (dermoid cysts), hamartomas, or choristomas involving the external ear.

INFLAMMATORY POLYPS

Inflammatory polyps occupying the external canal are not uncommon; however, practically all are related to chronic otitis media, originate in the middle ear, and present in the external canal through a drum perforation. This entity will be discussed in the section on Middle Ear Tumors. Rare inflammatory polyps could arise from the external auditory canal, particularly following an otitis externa, but origin from the middle ear must be assumed until it can be proven otherwise.

Tumor-like lesions of the external ear can develop in gout or calcinosis, but because of their rarity and systemic nature, they are not discussed further.

CYSTS OF THE EXTERNAL EAR

There are several types of cystic lesions described as occurring in the vicinity of the external ear and may be due to congenital malformation (preauricular cyst, first branchial cleft anomaly); true neoplastic proliferation (epidermal, sebaceous or dermoid cysts, pilomatrixoma); trauma (epidermal implantation cyst); or an unknown cause (idiopathic cystic chondromalacia, pseudocyst).

IDIOPATHIC CYSTIC CHONDROMALACIA (PSEUDOCYSTS)

This peculiar, usually painless, cystlike degeneration of the auricular cartilage, occurring mainly in young and middle-aged adults, has been described by Hansen. It is rarely seen bilaterally or in females (Santos et al.). The etiology is undetermined and the history does not support trauma. Clinically, the external auricular cartilage is enlarged (fig. 289) and the central cartilage area is distended by a watery, clear yellow fluid.

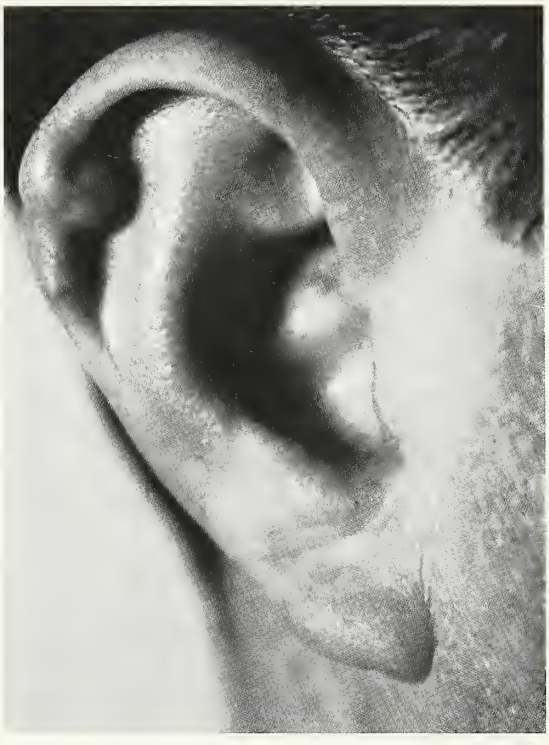

Figure 289
IDIOPATHIC CYSTIC CHONDROMALACIA
A 28 year old man had noted a slowly enlarging cyst on the helix of his right ear, which recently had become slightly tender.

Microscopically, there is no lining cell to the cystic spaces, nor are inflammatory cells characteristic. The surrounding cartilage is unremarkable. Although simple aspiration has been reported as curative, most cases quoted in the literature underwent a curettage-like removal. Differentiation from relapsing polychondritis may pose a problem because of the frequent initial presentation of relapsing polychondritis as a swelling of the external ear. The clinical pain and diffuse involvement of the external ear cartilage, the involvement of other cartilages of the body, and the systemic symptoms that are found in relapsing polychondritis (Damiani and Levine) serve to clarify the diagnostic problem.

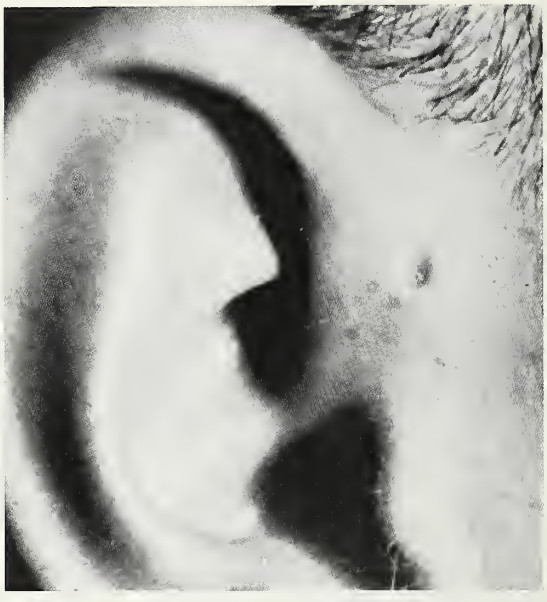

Figure 290
CONGENITAL CYST
A clinical view of the so-called preauricular pit, situated at the anterior crus of the helix. The depth of the tract averages between .5 and 1 cm, but it can extend into several centimeters and exit in the upper neck or middle ear cleft.

Congenital Cysts (first branchial cleft anomalies, preauricular pit, fistula auris congenita). There is some confusion as to the pathogenesis of these cystic lesions, but most writers concede that the majority of congenital cysts, as well as the related sinuses and fistulas that occur in the area of the external ear, are due to a first branchial cleft anomaly. Some have felt that the so-called preauricular pits (fig. 290), a small blind cutaneous tract of variable depth that is located along the anterior crus of the helix, is due to a failure of union between the hillocks that arise from the first and second branchial arches to form the auricle. Even though these latter lesions have a unique hereditary tendency, the acceptance of the formation of all congenital cysts, sinuses, and fistulas of the external ear areas from the first branchial cleft would conveniently explain the

development of all. In a sense, these congenital lesions are attempted duplications of the external auditory canal. Olsen and associates have classified the congenital lesions of the external auditory canal into cysts, sinuses, and fistulas. The cysts (fig. 291) which formed the majority of their series of 38 patients tended to form anterior to the ear and in relation to the parotid gland and possibly the facial nerve (Work's type II duplication). There was a 2 to 1 female to male ratio, ages ranged from 13 to 81 years (mean age 51 years), and either side was equally involved. The sinuses occurred in the pediatric patients, often with a postauricular cystic mass (Work's type I duplication), and the sinuses would follow the locations indicated in figure 292. The fistulas were essentially in children (fig. 293) and involved the same areas as the sinuses. The sinuses and fistulas were not sex related, but showed an affinity for the left side of the head. Either stratified squamous or ciliated respiratory columnar epithelium lined the cysts, with an occasional combination of the two. Lymphoid tissue with germinal follicles could be seen in the wall of most cysts. Sinuses and fistulas were lined by uniform stratified squamous epithelium except when destroyed by an inflammatory reaction. Occasionally, the cysts, sinuses, or fistulas that were lined by squamous cell epithelium contained subcutaneous tissue skin adnexa (fig. 294). Cartilage may also be seen in the wall of the branchial cleft anomalies. The main complication encountered with branchial cleft anomalies is that of infection. Surgery for complete removal should be done as soon as possible. Investigation should be made of the full extent of possible ramifications of the lesion as depicted in figure 292 and care taken to identify the facial nerve, which can have a variable anatomic relation with the first branchial cleft anomaly.

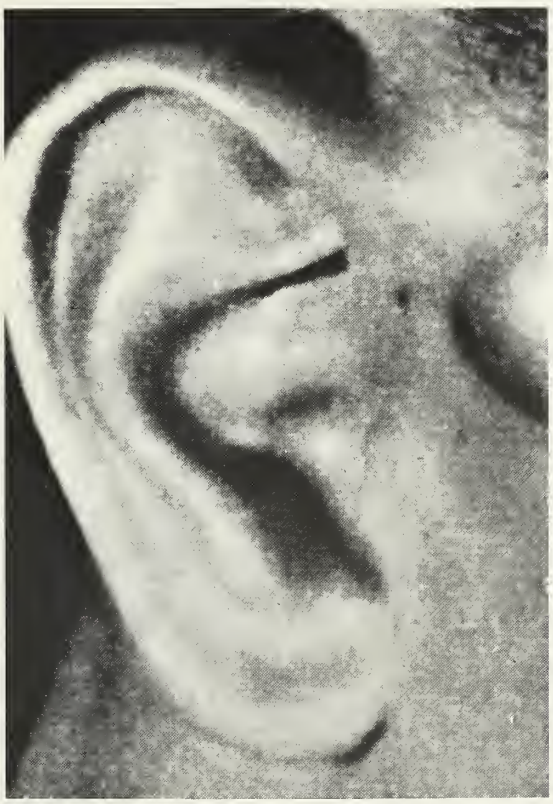

Figure 291
CONGENITAL CYST
This anterior auricular cyst represents a branchial cleft cyst, due to duplication of the first branchial cleft. (Fig. 19 from Becker, W., Buckingham, R.A., Holinger, P.H., Korting, G.W., and Lederer, F.L. Atlas of Otorhinolaryngology and Bronchoesophagology. Philadelphia: W.B. Saunders Company, 1969.)

Epidermal Cyst. This diagnosis is made essentially on a variable sized cystic structure lined by benign, uniform, keratinizing squamous epithelium with an adnexa-free subepithelial fibrous or areolar tissue zone. The lumen is filled with desquamated keratin unless replaced by inflammatory exudate. The epidermal cyst can be found as an isolated benign neoplasm in connection with the previously discussed branchial cleft anomalies or, possibly, as a result of trauma such as the implantation epidermal cyst (fig. 295).

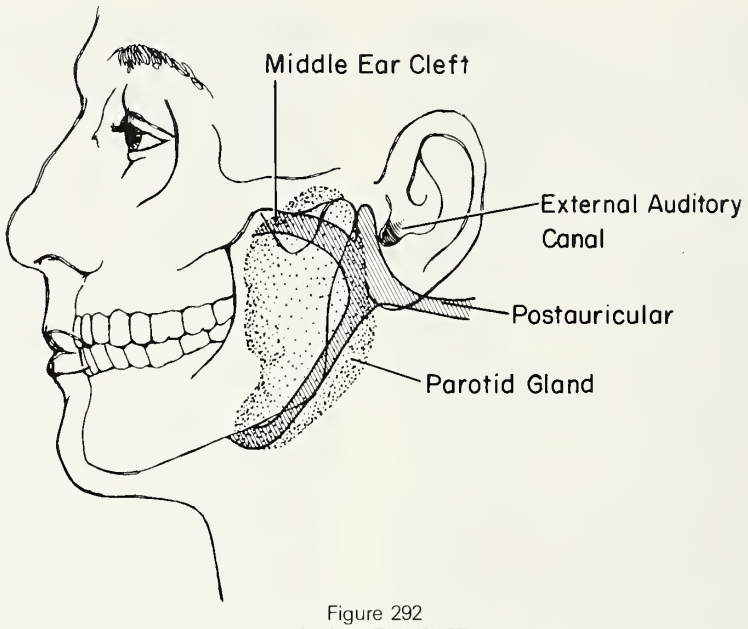

Figure 292
CONGENITAL CYST
This drawing represents the possible pathways that the sinuses and fistulas can follow in relation to the external auricle. The cutaneous opening or openings can occur anywhere along these tracts. (Adapted from Fig. 6 in Olsen, K.D., Maragos, N.E., and Weiland, L.H. First branchial cleft anomalies. Laryngoscope 90:423-436, 1980.)

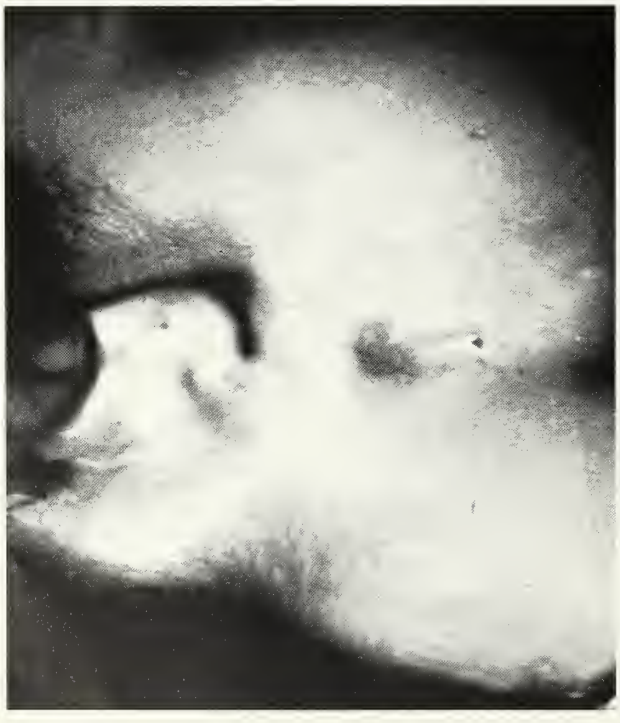

Figure 293
CONGENITAL CYST
This lesion, in a 21 year old woman, represents a sinus formed by a congenital duplication of the right first branchial cleft. A small intermittently draining opening had been present since birth, but had grown larger and seemed to drain more profusely in recent years. It connected with the middle ear space.

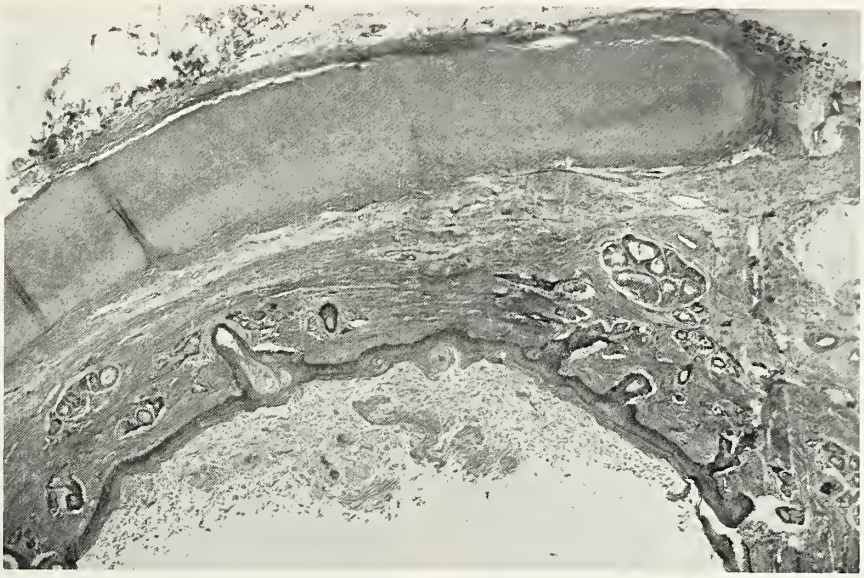

Figure 294
CONGENITAL CYST
A sinus draining anterior to the auricle that duplicates the histology of the external auditory canal (first branchial cleft). X25.

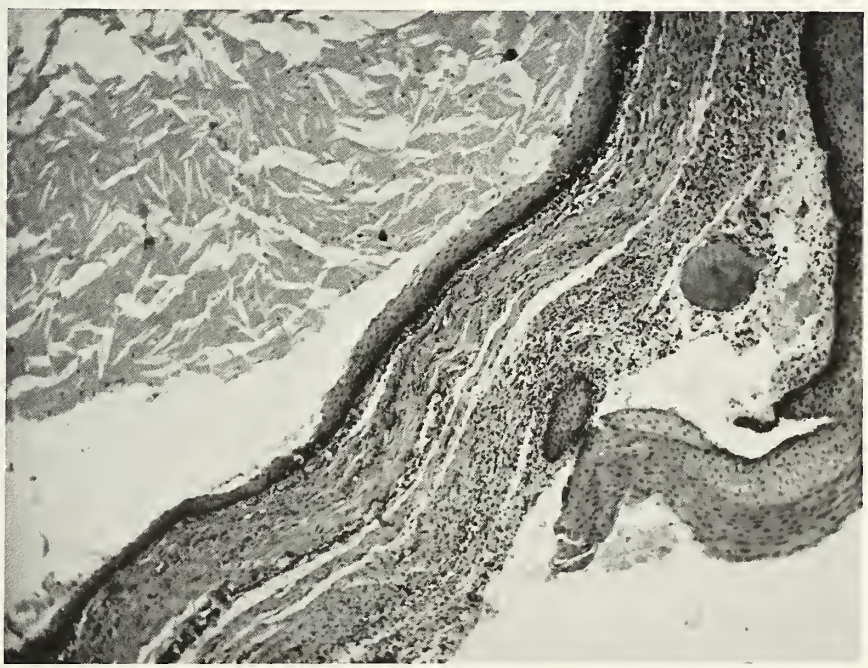

Figure 295
EPIDERMAL CYST
An epidermal cyst with the histology of a thin keratinizing squamous cell lining and a lumen filled with keratin debris. The surrounding tissue is unremarkable fibrous tissue with possibly inflammatory cell infiltrate. X63.

The sebaceous (pilar) cyst, a terminology usually mistakenly applied to the epidermal cyst, is a rare occurrence and is almost exclusively in the scalp (Graham et al.). The cyst may be lined by squamoid appearing epithelial lining which lacks the granular cell layer and intercellular bridges and presents an abrupt transition of the inner nucleated cell layer into anucleated cells forming the luminal material. Figure 20 reveals a lining formed in part by sebaceous cells admixed with squamous cells.

Cholesteatoma of the External Auditory Canal. This cystic lesion is distinct from the cholesteatoma of the middle ear spaces, which will be discussed later. The patient, usually over 40 years of age, will have a history of unilateral, chronic, dull ear pain, persistent otorrhea, and no hearing loss (Piepergerdes et al.). Clinically, there will be a localized sequestration of necrotic bone in the inferior or posterior inner half of the canal, with evidence of bone erosion and the possible recognition of an overlying pearly cystic structure. Histopathologically, other than necrotic sequestrated bone, a cystic lining of thin, benign, keratinizing, stratified, squamous epithelium may be identified. Treatment requires surgical removal of the cholesteatoma sac and the necrotic bone. This entity is not to be confused with keratosis obturans, a bilateral external canal condition, usually recurring in a younger aged group (below 40 years of age) with severe otalgia, mild conductive hearing loss, and a possible history of sinus disease or bronchiectasis. Pathologically, keratosis obturans is a diffuse squamous cell proliferation with marked surface hyperkeratosis of the canal skin with underlying inflammation and bone absorption. Rare dermoid cysts have been diagnosed in the external ear area.

Pilomatrixoma (calcifying epithelioma of Malherbe). The pilomatrixoma is a benign solitary cystic tumor more common in children and young adults, occurring predominantly on the face, neck, and arms, but with some affinity for the external ear (fig. 296). It probably arises from a primitive hair matrix cell. The lesion presents the clinical picture of a well demarcated epidermoid cystic structure with a lumen containing cheesy material. Microscopically, the often convoluted wall will be of varying thickness composed of small basaloid cells, sometimes separated by

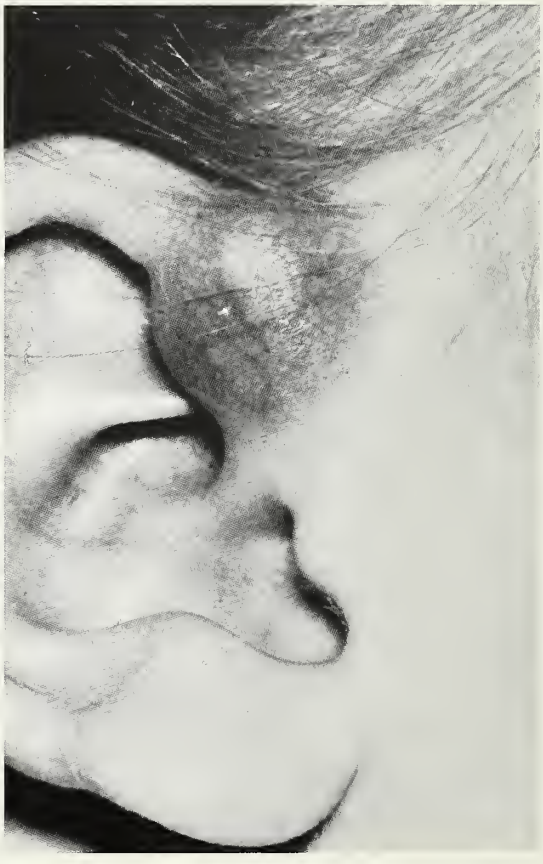

Figure 296
PILOMATRIXOMA
A gradually enlarging cystic structure in the external auricle of a 12 year old girl.

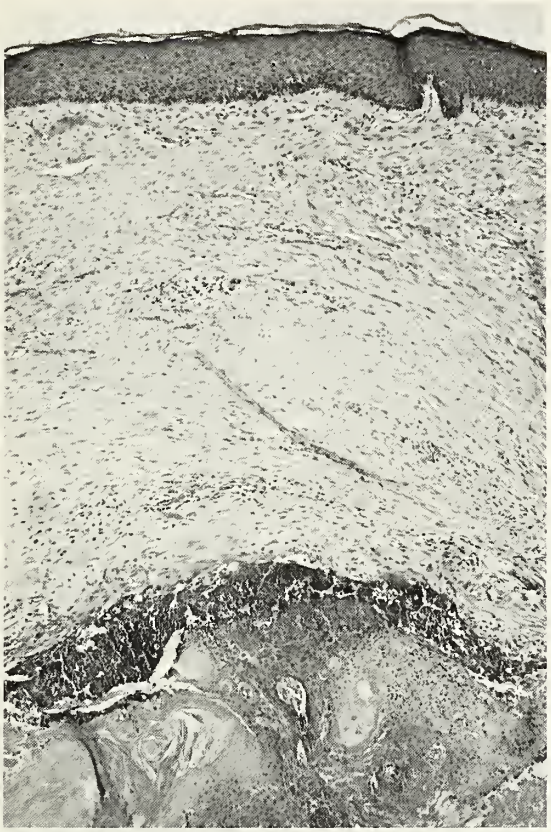

Figure 297
(Figures 297 and 298 are from the patient)
PILOMATRIXOMA
Low power view of a pilomatrixoma shows the well demarcated cystic structure containing keratinized cellular neoplasm. X25.

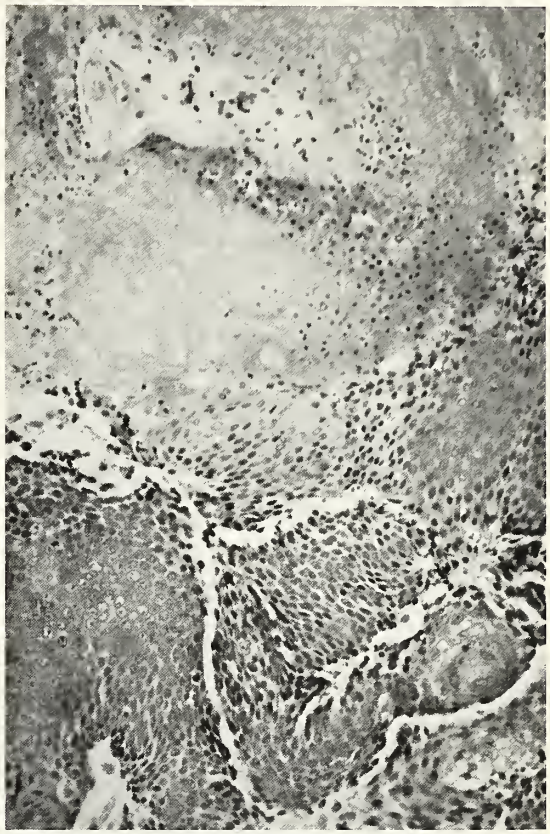

Figure 298
PILOMATRIXOMA
The compact basaloid type cells blend into the lumenal contents of the so- called shadow or ghost cells. X160.

connective tissue septa (figs. 297, 298). This layer will blend internally with a central zone of so-called shadow or ghost cells which contain a distinct cytoplasmic membrane, but have, seemingly, a degenerated cellular content. The central area of the lesion will also contain amorphous debris, keratin as well as a possibly calcified material. The treatment is usually total assured surgical removal; however, Lopansri and Nihm report the occasional aggressive behavior of the neoplasm.

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NEOPLASMS OF THE EXTERNAL EAR

An attempt will be made to classify neoplasms in the external ear area as strictly benign or malignant. For convenience, however, the ceruminal gland neoplasms, both benign and malignant, will be discussed together. Some neoplasms, such as the extra-adrenal paraganglioma, which may be primary in either the external or middle ear, will be discussed as part of the middle ear.

PAPILLOMA

This designation may mean any one of several specific entities, all of which would be considered a benign neoplastic proliferation of skin surface of the external ear. The squamous cell papilloma is the most common benign epithelial neoplasm of the external auditory canal listed in the AFIP-OTR (Table 25). This entity is a fungiform proliferation of uniform squamous cells with a central core of fibrous tissue (fig. 299) and grossly attached to the skin surface by a narrow stalk; however, a fibroepithelial polypoid tumor, with a prominent fibrous tissue component, is noted occasionally arising in the external ear canal (fig. 300). Sebaceous adenoma or papilloma, a benign neoplastic proliferation of the skin and/or its adnexa, will clinically imitate the squamous papilloma.

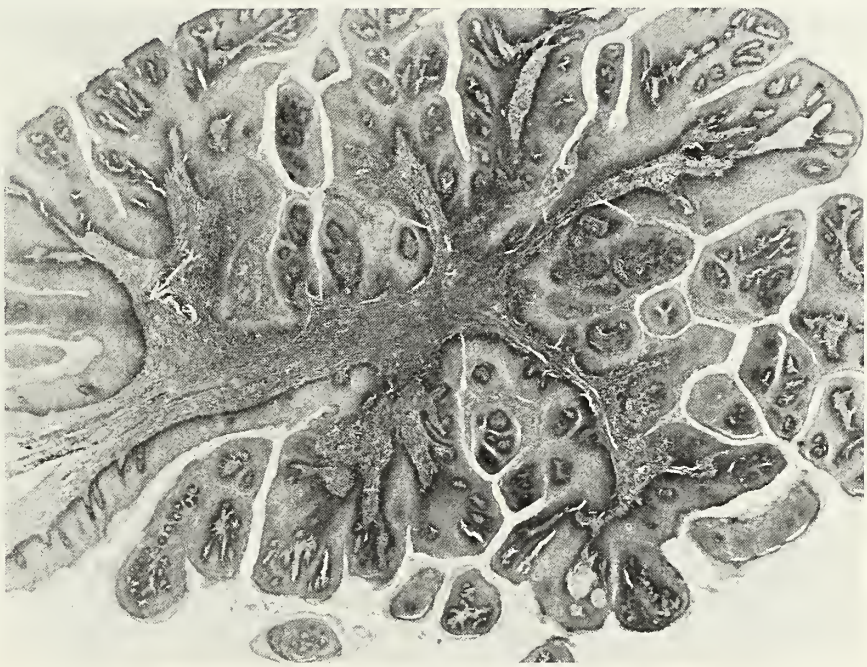

Figure 299
SQUAMOUS CELL PAPILLOMA
The typical histology of an exophytic squamous cell papilloma of the external ear shows fronds of uniform, benign, squamous proliferation with the central fibrous core. The narrow stalk of attachment is at the left. X50.

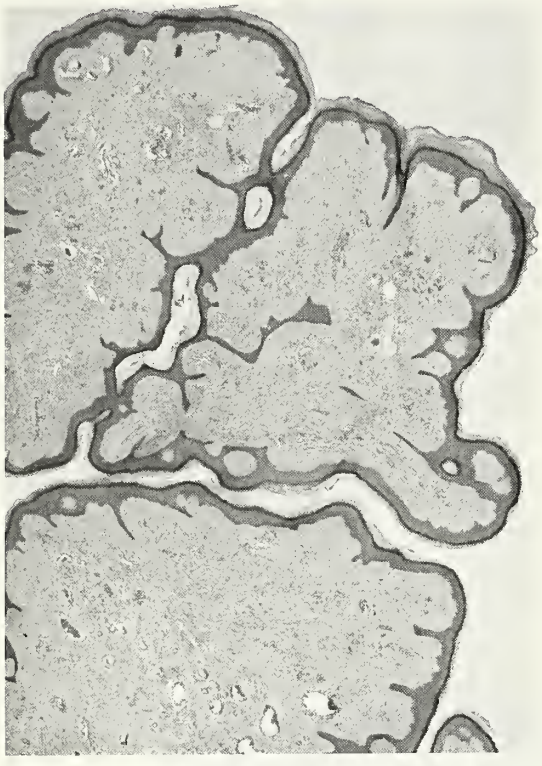

Figure 300
FIBROEPITHELIAL POLYPOID TUMOR
A low power microscopic view of a fibroepithelial polypoid tumor arising from the external auditory canal. X25.

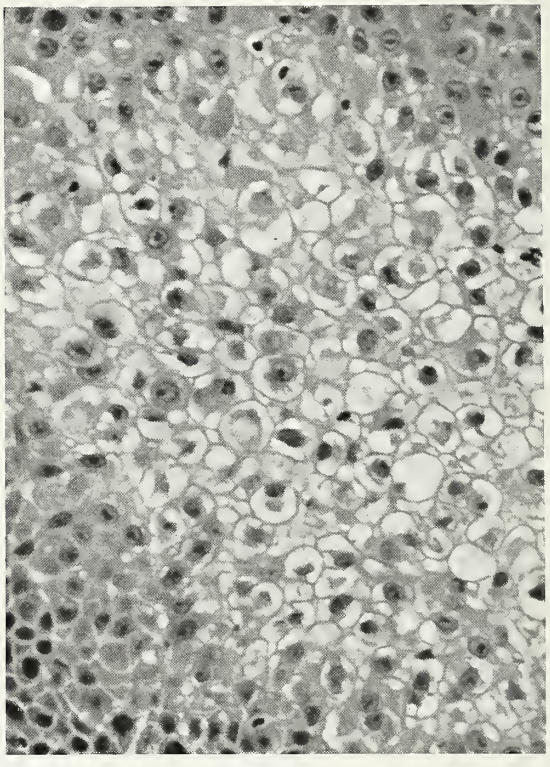

Figure 301
PAPILLOMA
This clinically papillomatous lesion of the external auditory canal combines features of a squamous cell and a sebaceous cell papilloma. X320.

One case each of sebaceous adenoma and papilloma involving the auricle and external canal are included in the AFIP-OTR (fig. 301). Therapeutically, the above mentioned two papillomatous neoplasms respond to simple complete removal. Some may be static in growth; however, surgical removal is the only assurance of an accurate diagnosis.

Seborrheic keratosis (basal cell papillomas) occurring in the middle-aged to early elderly individual are papillomatous proliferation of benign basaloid cells with a surface keratin proliferation. They consist of tan to brown, greasy macules or plaques suggesting a "stuck on" appearance. They can involve the auricle and the external canal. In spite of the reputation of easy removal and excellent prognosis, in recent AFIP-OTR material several cases arising from the external canal were shown to recur and undergo local aggression following what was thought to be adequate surgical removal. Verruca vulgaris and molluscum contagiosum, which can suggest papillomatous neoplasia clinically and pathologically, can involve the external ear. The reader is referred to texts of skin pathology for more information on these typical skin tumors.

OSTEOMAS AND EXOSTOSIS

These two entities, when involving the osseous portion of the external auditory canal, were felt in the past to be synonymous. Recent studies have supported their clinical and pathologic differences (Graham; Sheehy).

The osteoma of the external auditory canal is usually a solitary, unilateral, bony, pedunculated tumor attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line (fig. 302). In Sheehy's study, osteomas occurred in patients from 12 to 62 years of age, with 62 percent being under 50 years of age. Four of 16 patients were female. There was no definite relation to exposure to canal irritation, such as swimming. Symptoms were intermittent, mainly external canal obstruction. Occasionally they are discovered on routine examination.

The osteoma is covered by keratinizing stratified squamous cell epithelium and an underlying fibrous aglandular periosteum. The bone is lamellar in type, and may have an outer cortex and inner cancellous trabeculated architecture (fig. 303); the latter resembling normal marrow spaces with either hematopoietic, fat, or fibrous tissue. Occasionally, the osteoma will consist completely of compact (eburnated) bone.

Exostoses are four times more common in the external canal than are osteomas. They are broad-based hyperostotic, often multiple, lesions and are often bilateral and symmetric. In Sheehy's 64 patients with exostoses of the external auditory canal, only 3 were women. The ages ranged from 18 to 70 years, with 75 percent under 50 years of age. In 40 patients where information regarding swimming habits were available, 39 were frequent ocean swimmers. Intermittent obstruction was the major symptom in half of the 64 patients, 11 presented with a conductive hearing loss, and in an additional 40 percent, recurrent otitis externa was the initial symptom.

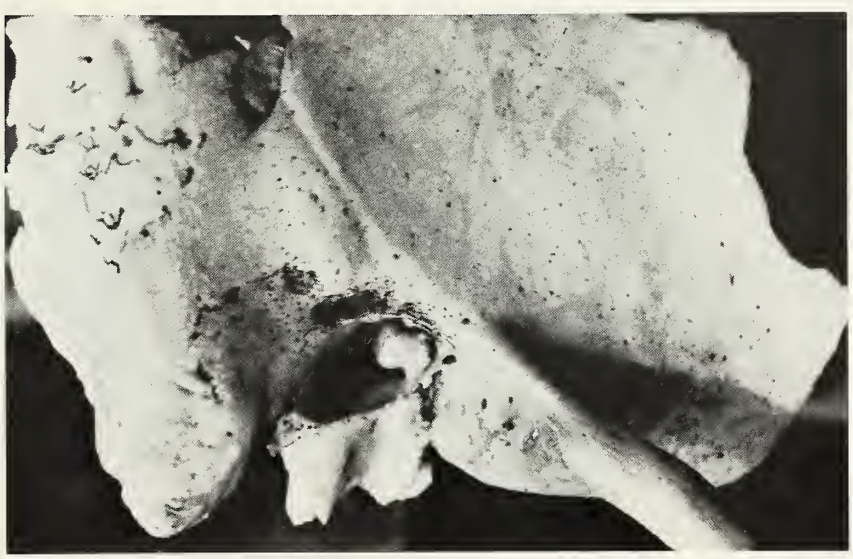

Figure 302
OSTEOMA
This temporal bone specimen demonstrates the typical anatomic location of the osteoma at the tympanomastoid suture line.

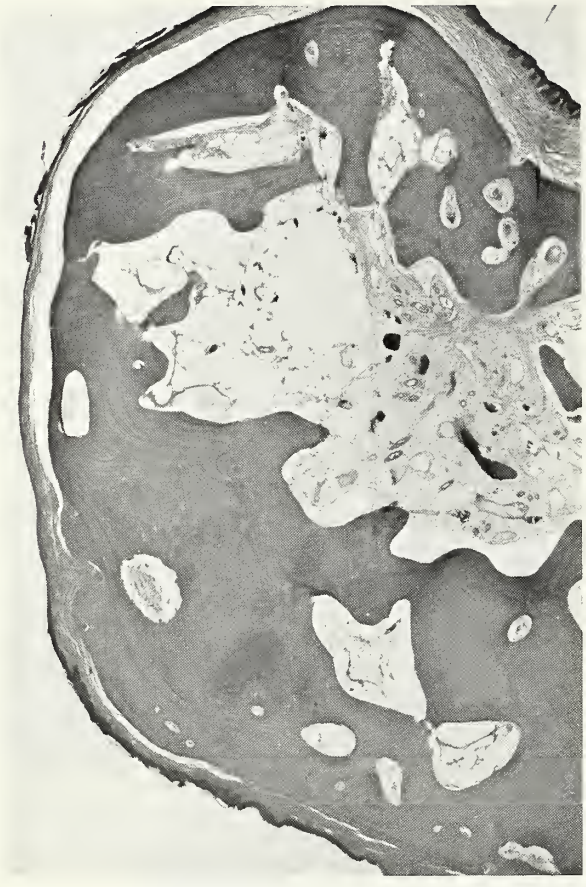

Figure 303
OSTEOMA
A projecting osteoma reveals an essentially normal bony cortex and cancellous interior marrow area filled with fibrous tissue. The attachment to normal bone is usually by a narrow neck. X25.

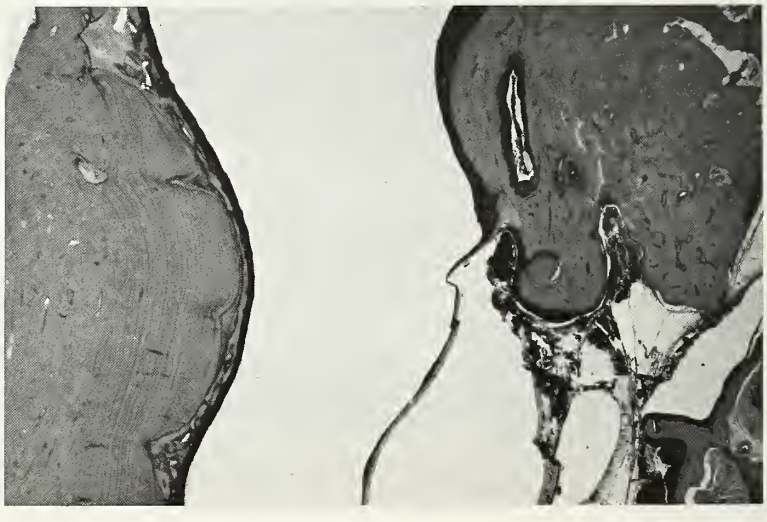

Figure 304
EXOSTOSIS
A low power view of the inner osseous auditory canal shows an exostosis on the left and a smaller one on the right. The suggested "heaped up" bone forming the mass suggests irritation of the periosteal layer of the normal bone. X25.

The surface is covered by epidermis with underlying periosteum of compact fibrous tissue. The bony component is composed of parallel layers of subperiosteal bone with no marrow-like spaces (fig. 304). The pathologic picture suggests an irritative reactive bony hyperplasia of the canal wall.

Sheehy recommended surgical removal of the osteoma through the external meatus, under local anesthesia. In the exostosis, surgical correction of the bony stenosis via a posterior aural approach is indicated only if the lesion is symptomatic.

As was intimated earlier in this section, any neoplasm of the skin has the potential to occur in the external ear. The medical literature as well as the AFIP-OTR contains isolated reports of vascular lesions as well as lipoma; chondroma; fibroma; dermatofibroma; fibroxanthoma; peripheral nerve sheath tumors (neurilemoma, neurofibroma); smooth muscle tumors; tumors of skin appendages; and auricular mixed tumors of salivary gland type. Nevi are quite common on the pinna and may be junctional, intradermal, or compound in type. The five patients with external auditory canal nevi listed in the AFIP-OTR revealed only the intradermal type histology.

ADENOMATOUS NEOPLASMS OF CERUMINAL GLAND ORIGIN

Definition. These neoplasms, both benign and malignant, arise from the modified cerumen- secreting apocrine sweat glands of the external auditory canal.

Confusion exists in the medical literature regarding a feasible histologic and clinicopathologic classification of external auditory canal ceruminal gland tumors. The overall opinion of published experiences and a study of the cases in the AFIP-OTR supports, for therapeutic and prognostic purposes, the idea of a histologic division into benign and malignant tumors. The classification in Table 27 is suggested.

Table 27

CERUMINAL GLAND NEOPLASMS
AFIP Otolaryngic Tumor Registry (1940-75)

	No. Cases
Benign	
Adenoma	25
Mixed tumor (pleomorphic adenoma)	9
Syringocystadenoma papilliferum	4
Malignant	
Adenocarcinoma	21
Adenoid cystic carcinoma	19

CERUMINAL GLAND NEOPLASMS

SYNONYMS AND RELATED TERMS: Hidradenoma; ceruminoma; sweat gland adenocarcinoma; malignant ceruminoma; ceruminal cylindroma.

Incidence. Although the literature of ceruminal gland neoplasms is scanty, there are approximately 80 cases reported, and the 75 patients contained in the AFIP-OTR material comprise 4 percent of all neoplasms of temporal bone contained in the AFIP-OTR.

Clinical and Gross. Ages varied from 12 to 87 years, with an average of 52 years (Hicks; Perzin et al.). There was male predominance in the adenoma and the adenocarcinoma, no sex preference in the adenoid cystic carcinoma, and female predominance in the mixed tumor type adenoma. Younger patients had a tendency to have more aggressive tumors. Symptom duration prior to tumor diagnosis varied from days to years, with the shortest history generally accompanying the malignant tumors. Complaints in patients with benign ceruminal tumors

were usually those of canal mass, canal blockage, hearing difficulty, and, rarely, an otic discharge, while the malignant tumors appeared to produce pain as the outstanding symptom. The gross feature was a skin-covered, round projection, usually into the outer half of the external auditory canal lumen. In the AFIP-OTR material, ulceration suggested a malignant tumor. Size varied from under 1 cm to 3 to 4 cm. The larger tended to involve the adjacent vital cavities. Clinical and anatomic evidence that an external ear area tumor originated from the nearby parotid gland served to eliminate it from this series of strictly primary external canal neoplasms.

Microscopic. The pathologic differentiation between the malignant ceruminal gland neoplasms should not prove difficult; but factors such as invasiveness and the clinical pattern of growth might occasionally be utilized in the proper histologic classification. One feature common to all ceruminal gland tumors is the lack of a definite capsule.

Adenomas reveal demarcation from surrounding tissue, with some tumors taking on a polypoid appearance. The glandular pattern may be quite varied, even in the same tumor. Multisized round glands or stellate-shaped epithelial lined spaces with intraluminal projections or folds may persist (fig. 305). The intervening stroma is usually variable amounts of unremarkable condensed fibrous tissue. An occasional adenoma shows a hyaline condensation at the periphery of cellular groups. Back-to-back glandular patterns are common. The epithelial component is essentially one of an inner cuboidal eosinophilic cell resembling the normal ceruminal secreting cell and often showing luminal secretory droplets. There is usually an outer circumferential cell layer of cuboidal to spindle cells exhibiting a scantier, sometimes darker cytoplasm and vesicular nucleus. This would seem to represent a myoepithelial element. Mitotic figures and pleomorphism are not characteristic. Intracytoplasmic ceroid or iron granules may or may not be demonstrated

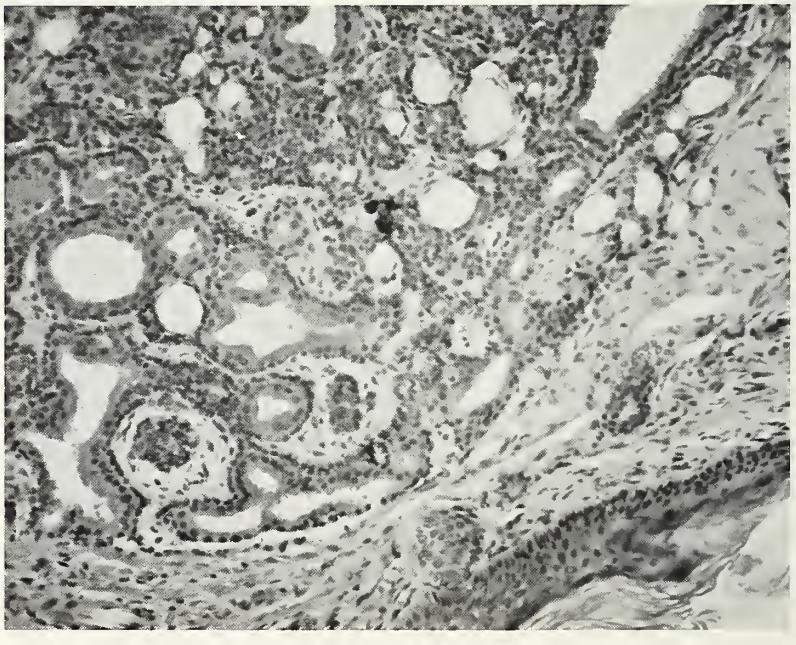

Figure 305
CERUMINAL ADENOMA
(MIXED TUMOR TYPE)
Note the close resemblance of the adenoma to the normal ceruminal gland. The neoplasm reveals a double layered gland pattern, with the inner layer demonstrating secretory activity. The outer layer of myoepithelial cells is more prominent than in the normal gland. X160.

(Wetli et al.; Cankar and Crowley). Diastase resistant PAS positive material and mucicarmine positivity have been demonstrated in tumor cells and the glandular lumen.

The mixed tumor type of ceruminal adenoma may be identical to that arising from salivary gland tissue with the usual variable ratio of tubular, glandular, or solid formations of epithelial cells in a chondroid or myxomatous matrix component (fig. 306). Occasionally, a portion of the tumor may have an area typical of the solid form of ceruminal gland adenoma (figs. 307, 308).

The syringocystadenoma papilliferum arising from the ceruminal gland is identical to that described in the skin elsewhere (Lever and Schaumburg-Lever). One or several cystic invaginations extend down from the canal skin with villus-like projections into the lumen. The surfaces of both the projections and cyst walls are lined by a double layer of epithelial cells characteristic of ceruminal or apocrine neoplasms (fig. 309).

Of the malignant ceruminal gland neoplasms, the slightly more common variety, according to the AFIP-OTR, is the relatively

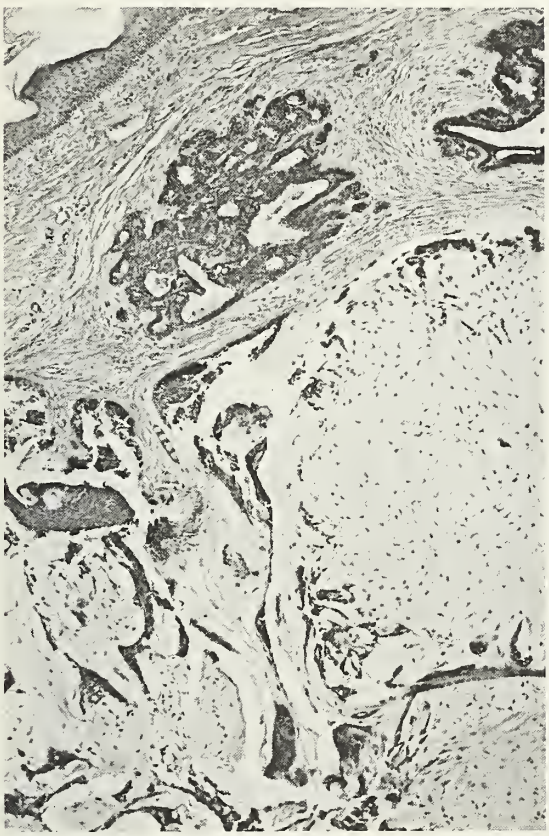

Figure 306
CERUMINAL ADENOMA (MIXED TUMOR TYPE)
This view depicts a prominent pseudochondromatous matrix, and a tubular epithelial element of a mixed tumor of salivary gland type. X25.

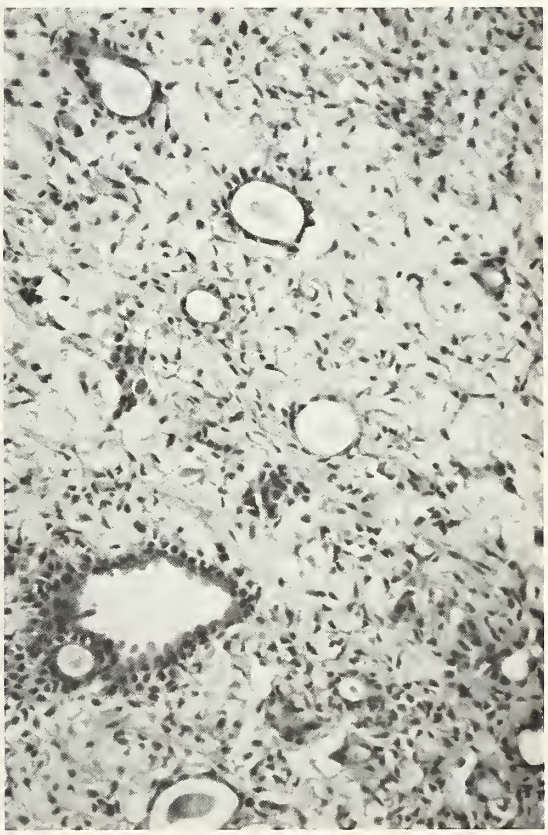

Figure 307
CERUMINAL ADENOMA (MIXED TUMOR TYPE)
This view of the pseudomyxomatous area of the mixed tumor type ceruminal adenoma contains a gland structure demonstrating apocrine secretion with cytoplasmic droplets within the lumen. X160.

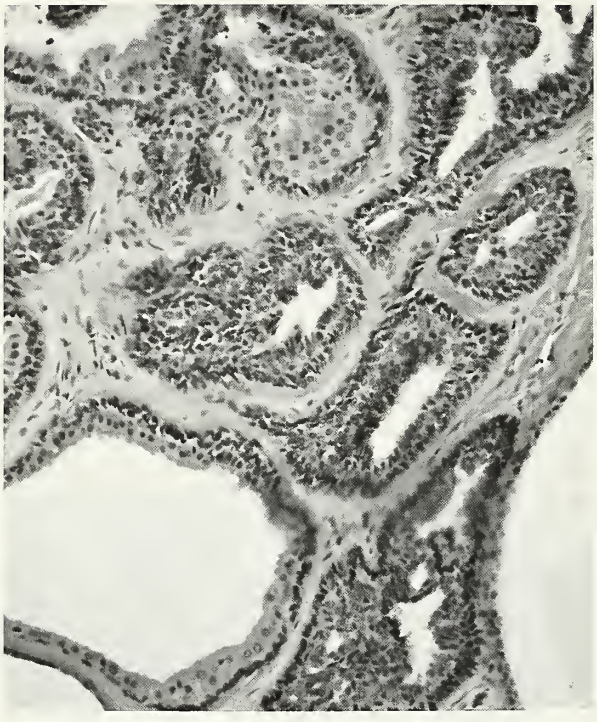

Figure 308
CERUMINAL ADENOMA (MIXED TUMOR TYPE)
In this mixed tumor type ceruminal adenoma, the epithelial element has an apocrine glandular appearance. X160.

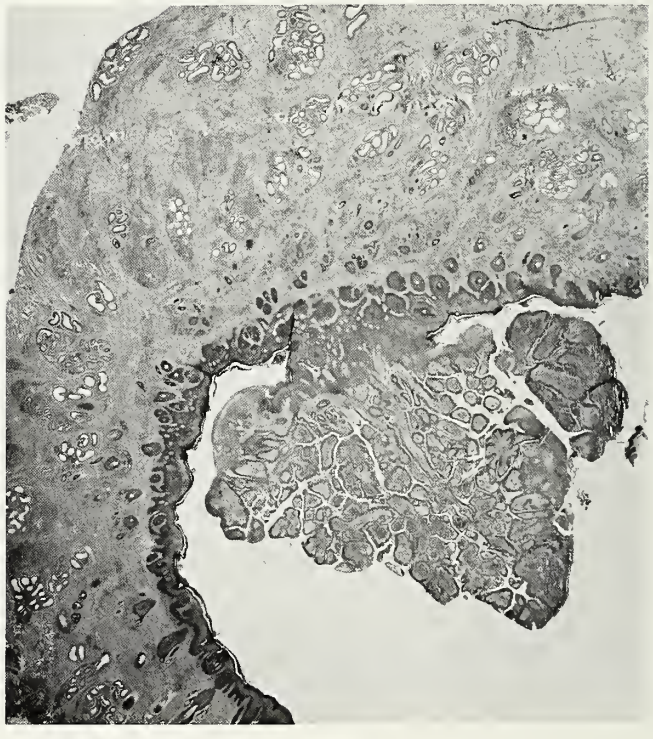

Figure 309
SYRINGOCYSTADENOMA PAPILLIFERUM
This is a scanning view of a syringocystadenoma papilliferum with the cystic invagination from the skin surface and with papillomatous projection from the cyst wall. The epithelium of the projection has a ceruminal apocrine morphology. X25.

anaplastic variant of the adenoma, the adenocarcinoma. Differentiation from the adenoma can be difficult and, if histopathologic characteristics such as pleomorphism, nuclear anaplasia, and mitotic activity are not convincing, evidence of clinical aggression may support the malignant diagnosis. The clinical and pathologic evidence is that of an infiltrating, poorly demarcated neoplasm. The adenocarcinoma will generally lose the double cell layer so evident in the adenoma and the cell morphology will be pleomorphic and have, possibly, mitotic activity (figs. 310-312).

An occasional report of a primary mucoepidermoid carcinoma of the external canal has appeared in the English medical literature, but these might be ceruminal adenocarcinomas with mucin production (fig. 313), or possibly the rare presentation of a primary parotid gland neoplasm in the external auditory canal.

An adenoid cystic structure is a distinctive characteristic of a significant portion of the malignant ceruminal gland neoplasms (fig. 314). The histologic pattern does not differ from the adenoid cystic carcinoma of salivary gland origin. The typical "cribriform" pattern

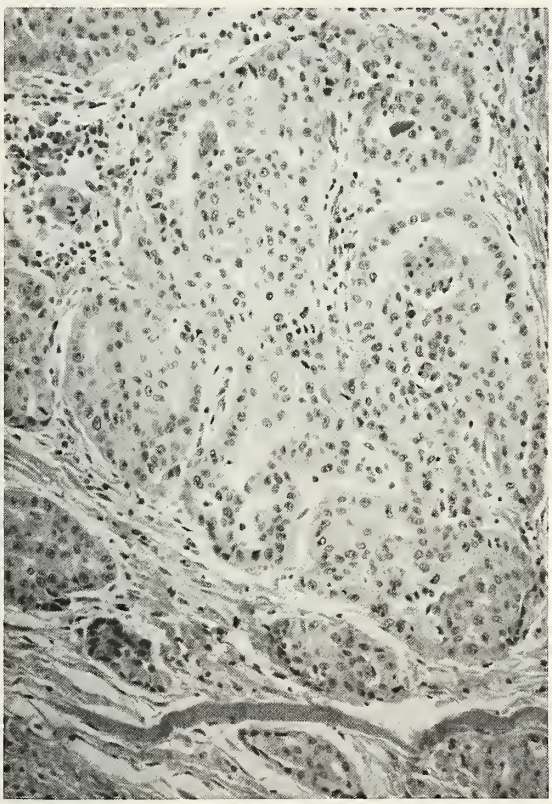

Figure 310
CERUMINAL ADENOCARCINOMA
Note the anaplastic cytology of the epithelial adenomatous neoplasm and that the double layered appearance of the ceruminal adenoma is absent. X160.

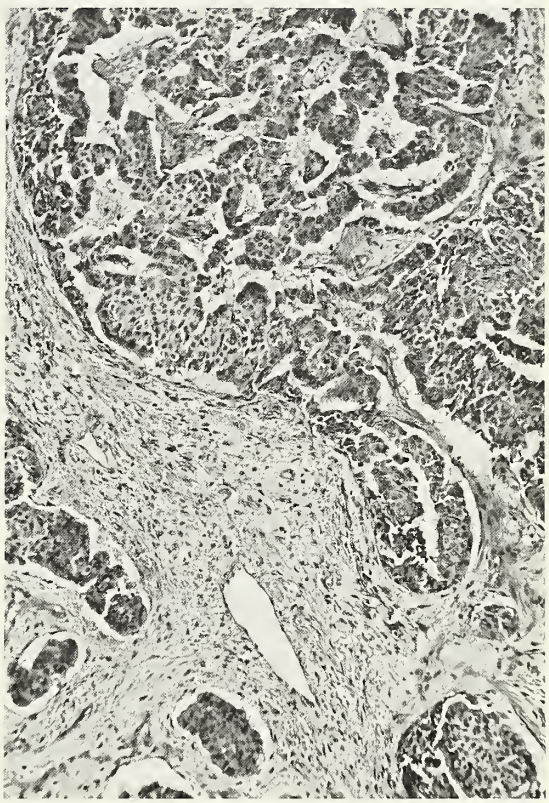

Figure 311
(Figures 311 and 312 are from the same patient)
CERUMINAL ADENOCARCINOMA
A more anaplastic ceruminal gland adenocarcinoma had rapid growth and infiltration to adjacent vital tissues. There was no metastasis. X100.

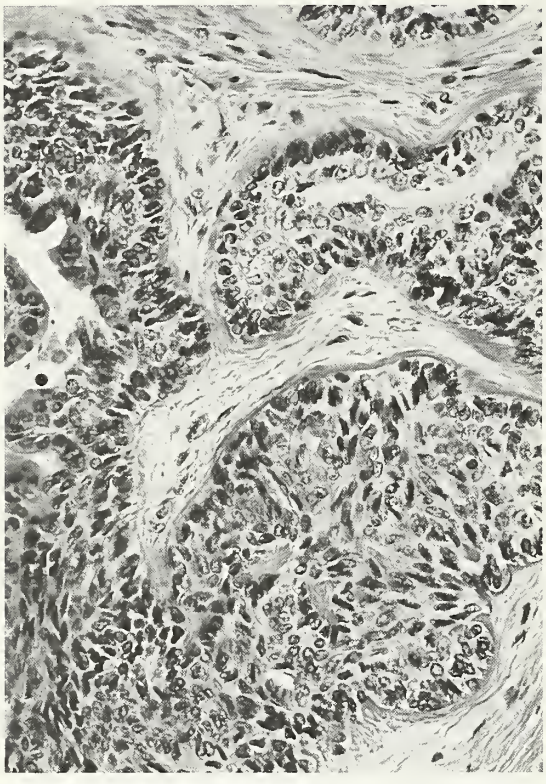

Figure 312
CERUMINAL ADENOCARCINOMA
Note the obvious increased anaplasia and mitotic activity. X200.

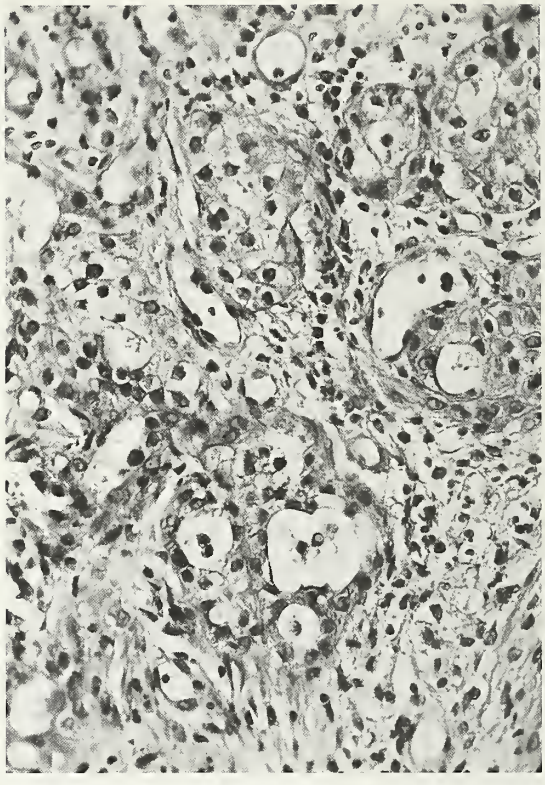

Figure 313
MUCOEPIDERMOID CARCINOMA
This primary external auditory canal adenocarcinoma has, in addition to a glandular morphology, mucus producing cells admixed with groups of epidermoid cells, qualifying it as a mucoepidermoid carcinoma. X200.

composed of small hyperchromatic cells lacking the glandlike polarization around the mucoid or hyalin filled spaces predominates. A solid or noncystic form may also be seen. A prominent infiltrative pattern including the involvement of perineural spaces is common.

The stroma of malignant ceruminal tumors is similar to that described in adenoma. Ceruminal gland adenocarcinomas may have the same histochemical findings noted for adenomas, but usually in less amount.

Natural History. The histologic classification of ceruminal gland tumors is definitely correlated with prognosis and morbidity. In the benign tumors, the only reported complication is the rare recurrence of the tumor following inadequate surgical removal. Of the malignant ceruminal gland tumors other than the adenoid cystic carcinoma variety, the main complication is recurrence following surgical removal (Pahor and O'Hara), usually with more extensive regional spread and occasional death due to involvement of adjacent vital structures. Metastasis in nonadenoid cystic type ceruminal adenocarcinoma is exceedingly rare (one patient contained in the AFIP-OTR data). In adenoid cystic carcinoma of ceruminal gland origin, aggression, metastasis, and death is much more common. Approximately half the patients

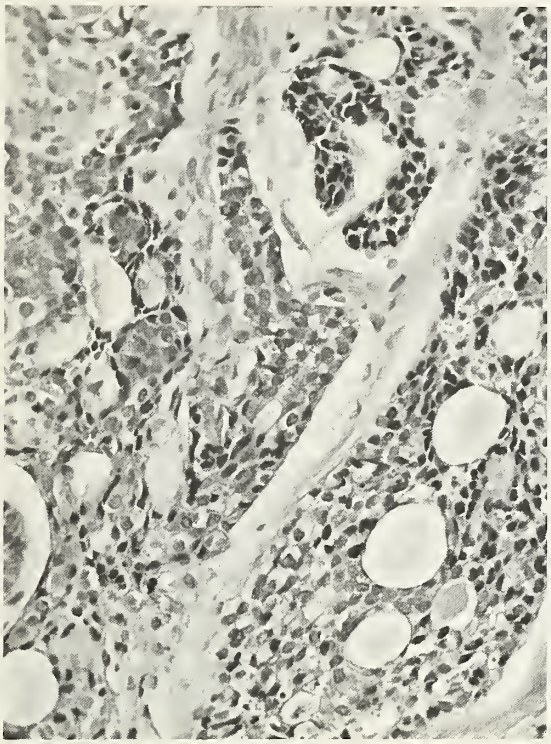

Figure 314
ADENOID CYSTIC CARCINOMA
The cribriform pattern and solid areas are emphasized in this adenoid cystic carcinoma of the external auditory canal. X200.

with this neoplasm are reported to have died of their disease (Perzin et al.; AFIP-OTR) due either to local aggressive spread or to distant metastasis.

Treatment. Complete removal is the recommended treatment of both benign and malignant ceruminal neoplasms. Such a therapeutic approach prevents recurrence in the former and is the main hope of cure in the latter. Radiotherapy has been only palliative, but has been used in combination with surgery with possible beneficial results in the malignant tumors.

Differential Diagnosis. Metastasis from regional (parotid gland) and distal sites (particularly the genitourinary tract) must be ruled out. The adenoma of the middle ear spreading through a perforated eardrum can be mistaken for a ceruminal tumor. There are no glandular structures of ceruminal type present in the middle ear to give rise to a ceruminal gland neoplasm in that anatomic site. Jugulotympanic paraganglioma and varieties of basal cell carcinomas may also pose diagnostic difficulties. In several instances in the AFIP-OTR experience, there has been a differential diagnostic problem in deciding between an adenoid cystic type ceruminal carcinoma of the external auditory canal and the benign eccrine cylindroma of sweat gland origin that may arise from the conchal portion of the auricle.

QUESTIONABLE MALIGNANT OR PREMALIGNANT EPITHELIAL NEOPLASMS OF THE EXTERNAL EAR

Keratoacanthoma

Keratoacanthoma is a squamous neoplastic proliferation, thought to be self-healing and arising from hair follicle origin, appearing predominantly on sun-exposed skin of elderly persons. Approximately 80 percent of the tumors arise on the face and 8.5 percent from the external ear (Patterson). Eleven cases of external ear origin, all apparently from the auricle, were contained in the AFIP-OTR material. The peak incidence is between 50 and 69 years, with a ratio of keratoacanthoma to squamous cell carcinoma of 1 to 3 (Patterson). It occurs twice as often in males as females, and is rare in blacks. Clinically, the mature lesion is a bud or dome-shaped, 1 to 2.5 cm, skin colored to pearly, erythematous nodule with a central, often umbilicated keratinous core. It may remain stationary for several months, but when regression does take place, it may require up to a year or longer for complete disappearance.

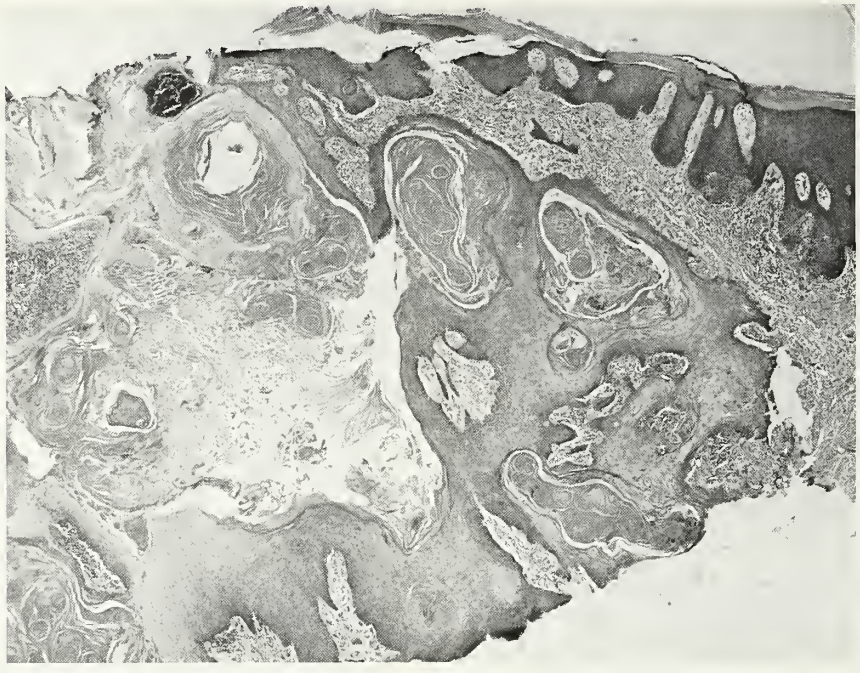

Figure 315
KERATOACANTHOMA
This shows the typical bowl-shaped architecture of a keratoacanthoma, with well differentiated squamous cell neoplastic proliferation forming the wall, and surface keratinization collecting in the central depression. X25.

Histology. Histologically, the central surface is filled with hyperkeratotic or parakeratotic material. The surrounding well differentiated, uniform, squamous cell proliferation is bowl-shaped (fig. 315), with surrounding dermal fibrous tissue usually containing a marked inflammatory cell infiltration. A problem facing the pathologist is that a biopsy taken from the edge of the keratoacanthoma can be quite difficult to differentiate from a well differentiated squamous cell carcinoma (fig. 316). With the reputation of self-healing, the best therapy would seem to be to let time take its course. However, because of the unsightly clinical lesions, the difficulty of microscopic diagnosis of a partial biopsy, and the occasional keratoacanthoma that has been reported to undergo malignant transformation (Patterson), the treatment of choice would seem to be complete excision of the lesion. This would satisfy cosmesis, a reliable diagnostic specimen, and would probably fulfill the expected treatment criteria of even the well differentiated squamous cell carcinoma.

Solar Keratosis

SYNONYMS AND RELATED TERMS: Senile keratosis; actinic keratosis.

Solar keratosis is generally accepted as the most common precancerous cutaneous epidermal disease of the skin-covered body surface (Graham et al.). The condition develops commonly on sun-exposed surfaces and particularly on aging, dry, wrinkled, and atrophic skin. The average age at clinical onset is 62 years. It is not sex related, but definitely is a disease of the fair complexioned caucasian. Clinically, the lesions are gray to deep brown,

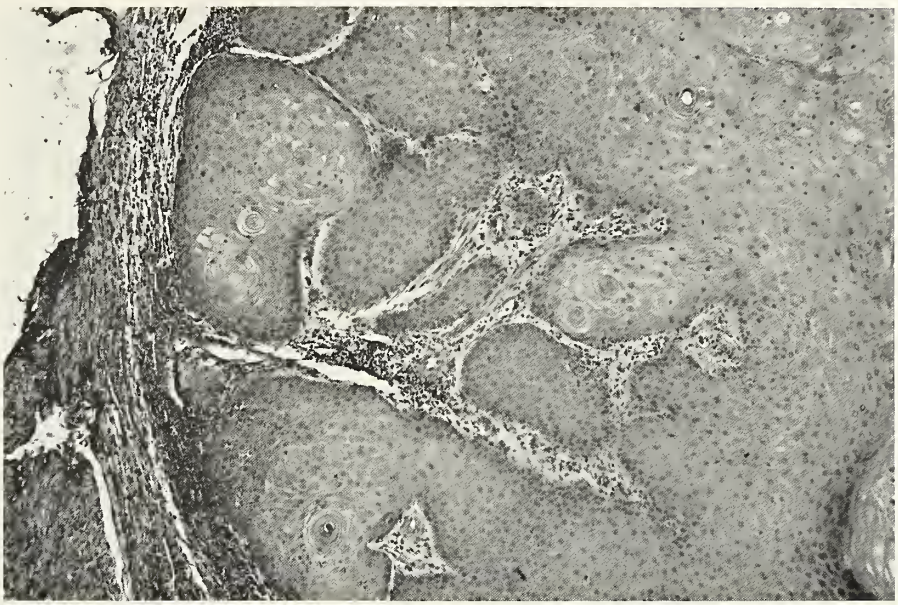

Figure 316
KERATOACANTHOMA
A biopsy of the edge of a keratoacanthoma demonstrates the difficulty in differentiating from a well differentiated squamous cell carcinoma. X160.

irregular in shape, scaly, keratotic, and usually flat-topped; however some are nodular, horny, or have a warty configuration. Histologically, there is a hyperplasia of the epidermis, with possibly elongated rete pegs, but with a dysplastic squamous cell proliferation in the basal area of the epidermis. In this latter area, it can be difficult to decide whether squamous cell carcinoma with early invasion has developed.

In the experience of the AFIP-OTR, solar keratosis can involve the pinna or the outer portion of the external auditory canal, particularly the meatus. Where the histology of a biopsy of the external canal area leaves doubt as to whether the histologic diagnosis is solar keratosis or squamous cell carcinoma, the wiser surgeon will do an assured complete removal of the lesion rather than merely rely on clinical observation. The habit of observation is certainly commendable on skin lesions that can be readily observed, such as on the external auricle. In the external ear canal, if a malignancy is overlooked or underdiagnosed, the recurrent aggressive behavior of such malignancy will usually involve a silent clinical extension into the middle or inner ear and, possibly, to the cranial cavity well beyond therapeutic help.

MALIGNANT NEOPLASIA OF THE EXTERNAL EAR

The cutaneous basal cell and squamous cell carcinomas of the external ear comprise 44 percent of all neoplasias listed in AFIP-OTR arising from the ear and the temporal bone area and account for 5 percent of all cutaneous neoplasms (Thawley and Penje). Other than the malignant adenomatous neoplasm of the ceruminal gland, discussed earlier, and malignant melanoma of the

pinna, there is little incidence of other than basal cell and squamous cell carcinoma arising in this anatomic area. Metastatic neoplasms will be discussed later. Nelms and Paparella quote a 52 to 84 percent neoplastic involvement of the auricle by malignant disease, 12 to 28 percent in the external canal area, and 15 to 22 percent in the middle ear. There is the rare primary sebaceous carcinoma or malignant vascular neoplasm (particularly Kaposi's sarcoma) involving the external ear. Also, chondrosarcoma, osteosarcoma, fibrosarcoma, leiomyosarcoma, lymphosarcoma, dermatofibrosarcoma protuberans, fibromyxosarcoma, and malignant fibrohistiocytoma are reported as isolated diagnoses. Because of their rarity in the external ear, these neoplasms need not be further discussed in this section; however, some have been presented in other sections of this Fascicle, as well as other appropriate Fascicles. Rhabdomyosarcoma is listed in the AFIP-OTR as arising clinically mainly from the external ear and, even though there may be the rare primary rhabdomyosarcoma of the auricle and external canal, the clinical evidence supports more an origin from the middle ear, with the initial symptomatology directed to the external auditory canal. Rhabdomyosarcoma has been discussed in the section on the upper respiratory tract tumors.

BASAL CELL CARCINOMA

SYNONYMS AND RELATED TERMS: Basal cell epithelioma; basalioma; rodent ulcer.

Basal cell carcinoma, a local infiltrative, rarely metastasizing neoplasm of dermal and adjacent skin adnexal origin, deserves special attention when originating from the pinna or external auditory canal. Its locally aggressive characteristics can have serious clinical implications, particularly in the area of the concha and external auditory canal, that may require comparatively radical therapeutic procedures.

Frequency, Age Distribution, and Etiology. In the AFIP-OTR there were listed 394 cases of basal cell carcinoma of the external ear area, with 330 cases primary in the auricle and 64 primary in the external auditory canal, accounting for 21 percent of all neoplasms of the ear and temporal bone. Bailin and associates, in 122 patients, demonstrated a 90 percent basal cell carcinoma and 10 percent squamous cell carcinoma ratio of involvement of the auricle. As to anatomic origin on the auricle in Metcalf's patients, 29 were on the posterior surface, 22 were on the helix and antihelix, and 10 each were located on the concha, crus, tragus, antitragus, and lobule. AFIP-OTR experience and a survey of medical literature support an 80 percent squamous cell carcinoma and 20 percent basal cell carcinoma involvement of the external canal, the basal cell carcinoma concentrating in the lateral auditory canal. Some published reports claim no sex predominance with the basal cell carcinoma of the external ear, while others support a 2 to 1 male to female ratio. The young adult is susceptible, but the average patient is in the sixth decade. Etiology suggests an actinic relationship. Involvement of nonwhites is rare.

Clinical and Gross. The most common clinical presentation is the noduloulcerative appearance (rodent ulcer), beginning as a small, pearly, waxy nodule that on further growth usually undergoes a central ulceration. The subcutaneous infiltration, except in large neglected tumors, is usually easily determined on surgical removal or gross specimen examination. In contrast to the more common "rodent ulcer" or solid type is morphea-like or sclerosing basal cell carcinoma occurring in 25 percent of basal

cell carcinomas of the external ear (Levine and Bailin), which is clinically a slightly raised, yellow plaque, sometimes ulcerating with a hemorrhagic surface. It is characterized by insidious subcutaneous infiltration not delineated on clinical or gross specimen examination. If adequate excision is not accomplished, recurrence and mutilation may be the outcome.

Microscopic. There are several pathologic types professed in the literature. The solid type forms the majority with variations, such as metatypical (basosquamous), adenoid-cystic, and keratotic, all of which behave essentially as the common solid type. The one exception is the morphea or sclerosing type described later. The common solid noduloulcerative basal cell carcinoma is characterized by various sized tumor masses rimmed by a peripheral layer of palisading of "picket fence" cells reminiscent of the basal cell layer of the normal epidermis from which the tumor may often be seen to arise. The major tumor is a compact formation of generally uniform oval nuclei with indistinct cytoplasm. Intercellular melanin pigment is rare. A varying desmoplastic (connective tissue) reaction is usually present. Surface ulceration may disturb the tumor architecture. The tumor infiltration is mainly in the form of wide, blunt pegs, but invasion by small, thin trabeculae of tumors cells is also seen.

The morphea-like or sclerosing type basal cell carcinoma is characterized by abundant sclerosing fibrous tissue in which there are thin strands of infiltrating basal type cells. The limit of tumor extension into adjacent subcutaneous tissue is difficult to evaluate histologically.

Natural History. Although basal cell carcinoma reputedly responds to adequate local surgery or irradiation therapy, its occurrence in the area of the concha of the external auricle or in the external auditory canal meatus can lead to a serious degree of extension into adjacent structures, which may not be appreciated by the patient or clinician. In neglected or inadequately treated patients, extension into the middle ear, mastoid, or even the cranial cavity is not uncommon. In the series of 29 patients with basal cell carcinoma involving the external canal and possibly spreading to the temporal bone, reported by Goodwin and Jesse, 20 percent were considered local treatment failure. In 71 patients with basal cell carcinoma of the pinna, Metcalf quotes a 90 percent, three-year cure rate and no metastatic disease. Therapy depends upon the clinician's expertise and the clinical extent of the disease. Surgery, irradiation, various dermatologic technics, including the MOHS technic and, rarely, chemotherapy, have been advocated.

SQUAMOUS CELL CARCINOMA OF THE EXTERNAL EAR

SYNONYMS AND RELATED TERMS: Epidermoid carcinoma; epithelioma.

This common malignant neoplasm attains special significance in the temporal bone area, particularly in the external auditory canal and middle ear because of its frequently advanced clinical stage before the diagnosis is established. Patients are sometimes treated for years for a draining ear, with the operating diagnosis of inflammatory external and/or middle ear disease. Biopsy examination has been the main reliable diagnostic tool. Squamous cell carcinoma originating from the external ear accounts for 24 percent of all squamous cell carcinomas of the head and neck region (Johnson and Helwig), with the majority occurring on the pinna. Shiffman noted that in 52 patents

with primary squamous cell carcinoma of the pinna, 27 arose on the helix; 11 on the posterior auricular skin surface; 6 on the antihelix; 3 each on the triangular fossa and concha; and 2 on the lobule. The AFIP-OTR lists 462 cases of squamous cell carcinoma of the external ear. The average age at diagnosis was 65 to 70 years for the pinna lesions, and 52 to 55 years for the external canal tumors (Johns and Headington; Lewis).

Pathogenesis. Squamous cell carcinoma of the external auricle and auditory canal quite often accompanies skin malignancies and malignant keratosis elsewhere in the patient. Actinic overexposure and frostbite appear to have a definite relationship. The trauma of spectacles and headgear to the auricle and chronic inflammation, carcinogen-producing bacteria, and irradiation exposure (Johns and Headington) to the external auditory canal have been suggested as causative agents.

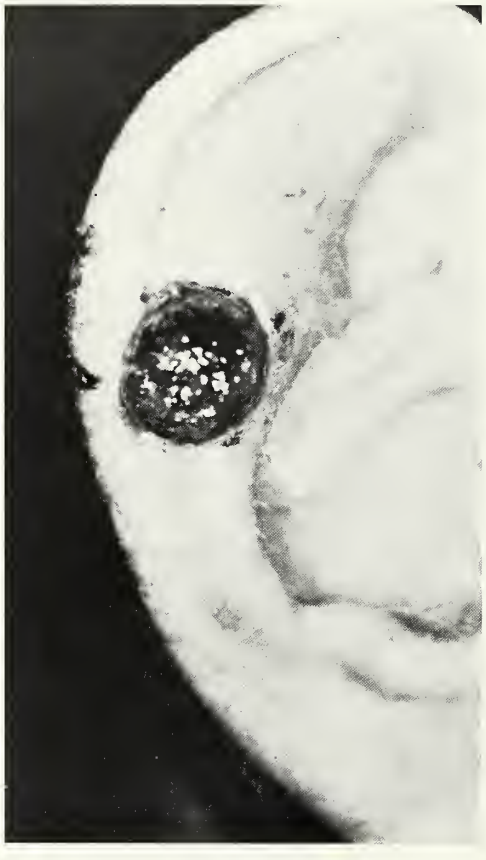

Figure 317
SQUAMOUS CELL CARCINOMA
An elderly man had a rapidly growing sore, with a raw, beefy, firm appearance, of his right external auricle. This is a squamous cell carcinoma.

Gross. Squamous cell carcinomas of the pinna do not vary in appearance from those of the skin elsewhere and usually begin as indurated, scaly, maculopapules resistant to casual therapy, and progress to enlarging, ulcerating, grossly aggressive-appearing neoplasms (fig. 317). Primary involvement of the external auditory canal is usually characterized by a scaly, oozing, or bleeding nodular to plaquelike, sometimes polypoid mass (fig. 318). Because of the limitation of visualization of the external canal, gross appearance is not particularly diagnostic.

Microscopic. The obvious microscopic diagnostic criteria of squamous cell carcinoma are usually present, including keratinization with intercellular bridges (fig. 319). Any degree of histologic differentiation may be encountered, but the majority of the AFIP-OTR patients with squamous cell carcinomas of the auricle and external auditory canal revealed a generally easily recognized squamous cell morphology tending to be moderately to well differentiated.

Natural History and Treatment. Distal or regional metastatic spread of squamous cell carcinoma of the pinna is 15 percent, and in the auditory canal it increases to 30 percent. The prognostic evaluation depends essentially upon the local extension of the neoplasm. Early recognition and definitive removal of neoplasms localized to the pinna and outer portions of the external canal have generally

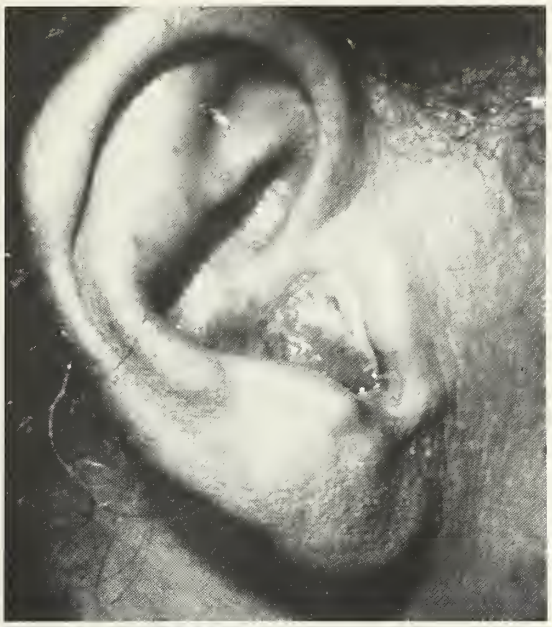

Figure 318
SQUAMOUS CELL CARCINOMA
A middle-aged female had had a history of earache of increasing severity, as well as deafness and drainage, for over a year. The neoplasm had destroyed practically all the middle and inner ear and was threatening invasion into the cranial cavity.

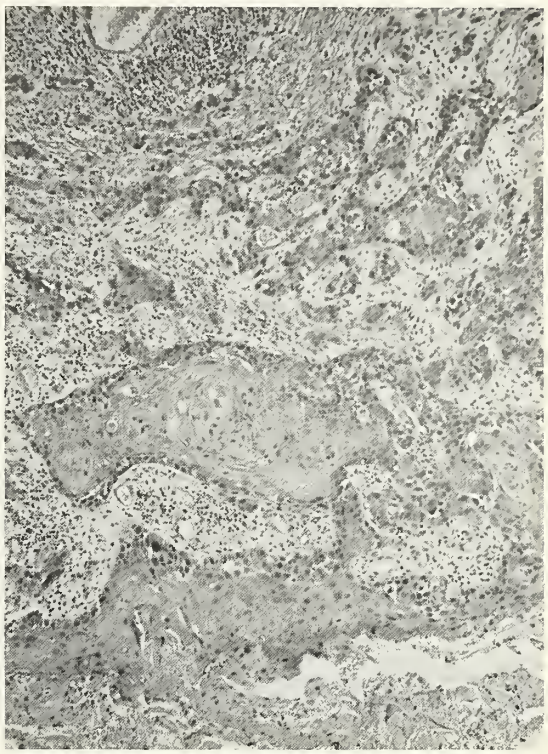

Figure 319
SQUAMOUS CELL CARCINOMA
This squamous cell carcinoma of the external ear demonstrates a well differentiated cytology. An occasional poorly differentiated squamous cell carcinoma can arise in this anatomic area. X63.

had a good prognosis. Johns and Heading-ton reported that of 20 treated patients with primary external auditory canal involvement, 10 are living, with 3 having recurrent disease 3, 6, and 12 years after treatment; 7 are free of disease 3 to 13 years following diagnosis; and 10 patients died of disease 1 month to 1.5 years following diagnosis. Goodwin and Jesse published an overall 75 percent treatment failure in squamous cell carcinoma of the external ear. Shiffman, in a series of 52 patients with squamous cell carcinoma of the skin of the pinna, quoted a treatment failure of 19 percent. Chen and Dehner revealed tumor related death in 1 of 17 patients with primary squamous cell carcinoma of the auricle, and in 11 of 21 with those arising from the external canal. Treatment of squamous cell carcinoma of the external ear will depend on extent of disease, presence of metastasis, and, possibly, the histologic grade. Surgery alone or with radiotherapy and/or chemotherapy, or radiotherapy alone have been utilized.

Adenoid squamous cell carcinoma (adenoacanthoma) of the skin (Johnson and Helwig) is a tumor pattern that is known to involve the ear (both auricle and external auditory canal) and, fortunately, is only of low aggressiveness with rare metastasis. Microscopic examination reveals a nodular proliferation of differentiated squamous-like cells from overlying epidermis into the underlying subcutaneous tissue. The identifying feature is the prominent adenoid to

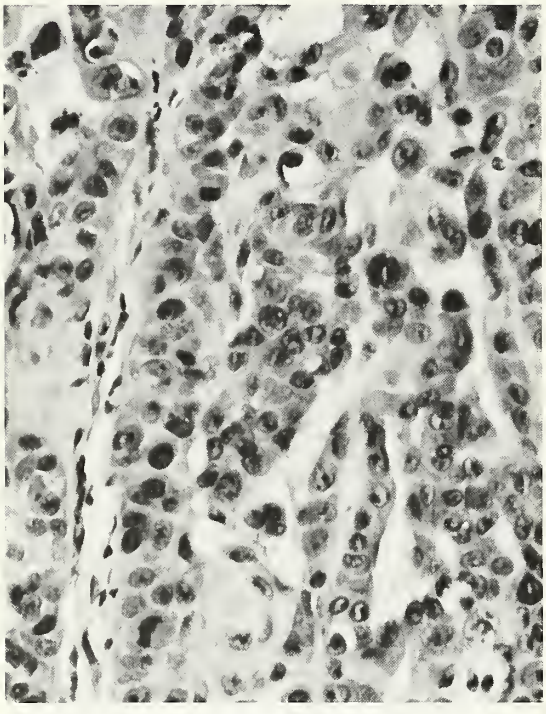

Figure 320
ADENOID SQUAMOUS CELL CARCINOMA
Higher magnification of an adenoid squamous cell carcinoma emphasizes the cleft or spaces separating the keratinizing squamous cell carcinoma. X320.

glandular pattern of the squamous cell proliferation, which is due to an apparent defect in the cohesion between the squamous cells (fig. 320). Assured local removal is therapeutically recommended.

MALIGNANT MELANOMA OF THE EXTERNAL EAR

Malignant melanoma of the external ear comprises 7 to 14.5 percent of all head and neck melanomas (Pack et al.; Byers et al.) and 6.7 percent of all melanomas treated at the Pack Medical Group from 1930 to 1965. Pack and associates and Byers and colleagues reported occurrence only on the external auricular anatomic area. The AFIP-OTR material does not contain a primary

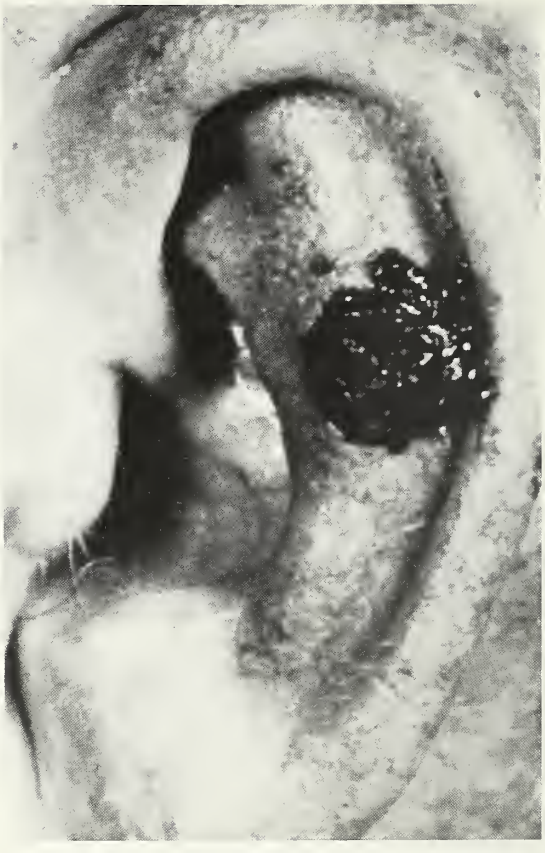

Figure 321
MELANOMA
This external auricle melanoma is of the superficial spreading type with early satellitosis.

external auditory canal melanoma. The five nevi from the canal that were listed were unremarkable intradermal nevi. Pack and associates suggested that all pigmented lesions of the external ear are rare when compared with the frequent occurrence on the remaining cutaneous surfaces of the body. Malignant melanomas of the external ear are usually of the superficial spreading type (fig. 321), which is characterized by an array of colors ranging from tan-black to brown to blue-gray to pink (Senturia et al.). Metastasis usually is primarily regional to lymph nodes of the upper part of the neck and

parotid gland or, according to the location on the pinna, to mastoid and occipital lymph nodes and even, occasionally, the lymphatic vessels of the external auditory canal. Of 42 patients with malignant melanoma of the external auricle, Pack and colleagues reported 33 percent with regional lymph node metastasis on the initial visit. In this same series, the age range was 7 to 81 years, with the average 49.6 years. There was a 3 to 1 ratio of males to females. The patients characteristically had red or blond hair, fair skin, and hazel or blue eyes.

Histopathology of malignant melanoma is discussed in the Fascicle of Tumors of the Skin.

Extent of the surgical approach, as well as the survival, is correlated with sex, clinical appearance, anatomic site, microscopic thickness (Breslow), level of invasion (Clark et al.), and presence of nodal metastasis. At the most, irradiation and chemotherapy has proved only palliative.

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TUMOR-LIKE LESIONS AND NEOPLASMS OF THE MIDDLE AND INNER EAR

Tumor-like lesions, especially the inflammatory tumors (cholesteatomas, cholesterol granulomas, and inflammatory polyps), are detailed here because the general surgical pathologist may not appreciate the significance of these lesions.

In Table 28 there is no attempt to classify the true neoplasms of the middle ear as benign and malignant, because a usually localized neoplastic process, such as a paraganglioma, can kill with local destruction and even metastasize. The same local fatal aggression can occur in benign neoplasms, such as the acoustic neuroma and the extracranial meningioma.

There are neoplasms, both benign and malignant, which are an important part of the spectrum of temporal bone pathology, such as histiocytosis "X"; fibrous dysplasia; ossifying fibroma; osteoblastoma; chondroma; chondrosarcoma; osteosarcoma; lymphoma; osteosarcoma; sarcoma (particularly rhabdomyosarcoma); malignant peripheral nerve tumors; fibromyosarcoma; and fibrosarcoma. They are discussed in the section on Tumors of the Upper Respiratory Tract.

Table 28

CLASSIFICATION OF MIDDLE AND INNER EAR TUMORS

Tumor-like lesions
Otic polyp
Cholesteatoma (keratoma)
Cholesterol granuloma
Encephalocele (ectopic central nervous system)
Teratoma, hamartoma, choriostoma
Neoplasms
Jugulotympanic paraganglioma
Meningioma (extracranial)
Acoustic neurilemoma (schwannoma)
Papilloma of the middle ear
Adenoma of the middle ear
Adenocarcinoma of the middle ear
Squamous cell carcinoma
Metastatic neoplasia to the middle ear region

TUMOR-LIKE LESIONS OF THE MIDDLE EAR

INFLAMMATORY POLYPS OF THE MIDDLE EAR

Clinically, inflammatory polyps present in the external auditory canal usually have their origin from the middle ear mucosa as a result of chronic otitis media accompanied by drum perforation. In chronic otitis media, buildup of chronic granulation tissue can lead to the formation of this proliferating polypoid tissue mass. Rarely, a granulation tissue polyp, such as a granuloma pyogenicum, will originate from the external auditory canal wall as a result of canal inflammation. When there is a polyp in the external auditory canal, particularly in the pediatric age group, it is imperative that neoplasia of the temporal bone area be ruled out with such diagnostic examinations as radiographic study. The gross appearance of the polyp is usually not diagnostic of an inflammatory genesis; however, histology will reveal a stroma consisting of various patterns of inflammation from edematous myxomatous tissue massively infiltrated with neutrophils to a more chronic pattern of chronic scar tissue with variable vasculature. Frequently, there may be giant cell granulomatous reactions, and an agent such as fungi, acid fast organisms, and even occasional parasites and spirochetes should be ruled out by special histologic studies. Identifying the site of origin as from the middle ear is aided by finding that the surface of the polyp in the more acute cases of otitis media may be a pseudostratified, columnar, ciliated epithelium characteristic of the inflamed middle ear mucosa. In more chronic middle ear infection, the polypoid tissue may reveal a metaplastic squamous cell mucosa.

Also in inflammatory polyps of middle ear origin, cystic inclusions of mucosa may be noted in the stroma, which should not be mistaken for neoplasia (figs. 322, 323). Of help in differentiating these inflammatory cysts from adenomatous neoplasia is the occurrence of tall, ciliated, columnar cells lining the cystic inclusions that would support a benign mucosal type cell.

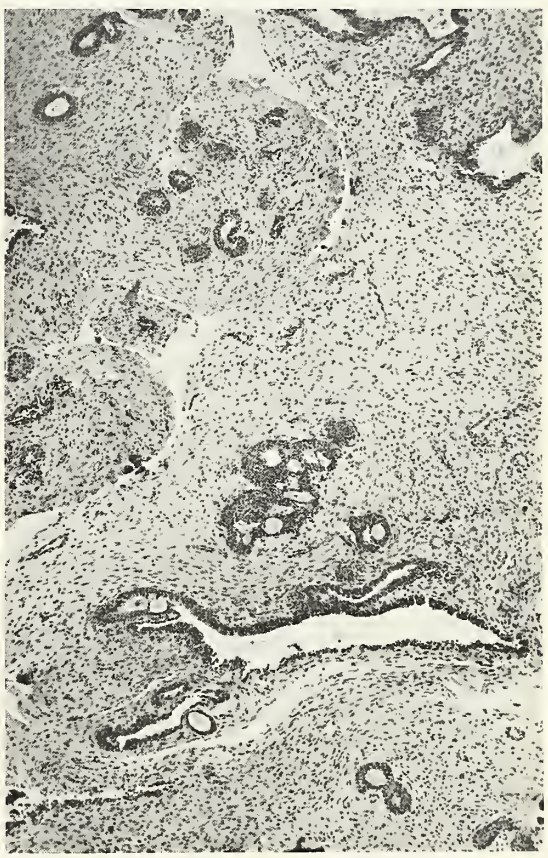

Figure 322
(Figures 322 and 323 are from the same patient)
INFLAMMATORY POLYP
A biopsy of hyperplastic chronic granulation tissue from chronic otitis media reveals numerous glandlike structures which are mucosal inclusions arising from the irregular lining mucosa. X63.

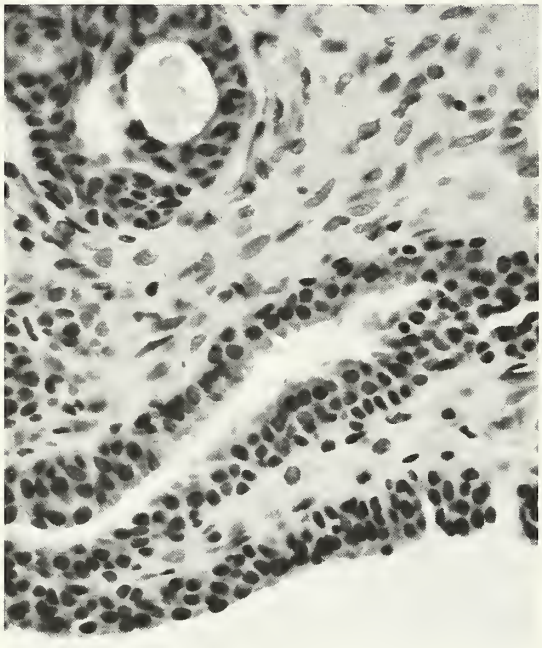

Figure 323
INFLAMMATORY POLYP
Note that these epithelial glandlike structures are reactive. There are cilia seen on the slit- like tubular structure arising from a space representing the middle ear. X160.

CHOLESTEATOMA

SYNONYMS AND RELATED TERMS: Keratoma; epidermal cyst; epidermoid; pearly tumor.

Definition. Cholesteatoma is usually considered a postinflammatory pseudotumor of mainly the middle ear spaces. It is, however, infrequently classified as a primary lesion (congenital cholesteatoma). This latter type results when it arises from an embryonic inclusion of squamous epithelium in the temporal bone and not as the result of an antecedent inflammation.

Incidence. Age at diagnosis can range from birth to 80 years, but it is more often noted in the third and fourth decades. There is no race predilection.

Histogenesis. The formation of cholesteatomas via the neoplastic or metaplastic proliferation of middle ear mucosa has been for the most part discarded, except for Sade, who suggested a metaplasia of the cuboidal epithelium of the middle ear to an epidermoid histology which then forms a cholesteatoma. The majority of authors favor an epidermoid epithelial migration theory following an otitis media. There is disagreement whether the migration occurs from the external canal or the external drum surface through a central or marginal perforation of the drum, or whether the intact drum, particularly in the superior area (Shrapnell's membrane, pars flaccida), retracts into the middle ear space as a cystic inclusion. Probably both methods may come into play in individual patients, but the percentage utilizing each is not known. A proven, but apparently rare, mechanism of postinflammatory cholesteatoma formation is the proliferation of the basal cell layer of the outer stratified squamous epithelial surface of the intact drum through underlying subepithelial fibrous tissue into the middle ear space. The noninflammatory or so-called congenital cholesteatoma forms from

1 to 7 percent of all temporal bone cholesteatomas, according to surveys of several published series.

Clinical. The lesion evolves, most commonly, in the middle ear and, less frequently, in the epitympanic space, the mastoid cavities, and the petrous portion of the temporal bone. The petrous portion is a common site of congenital cholesteatomas. The osteolytic effect of cholesteatoma can result in dramatic destruction of bone with extension of the cholesteatoma into adjacent vital cavities, such as the cranial spaces and the neck (Nager; Kreutzer and DeBlanc), with an occasional fatal outcome. The bony destruction is due to an enzyme, collagenase, which is a product of the squamous epithelium and subepithelial fibrous tissue of the cholesteatoma. Both the epithelium and fibrous tissue must be present for the collagenase to effect its osteodestructive properties. No evidence supports a definite transformation of cholesteatoma into a squamous cell carcinoma; however, the squamous cell carcinoma may occur in longstanding chronic otitis media (see section on Squamous Cell Carcinoma of the Middle Ear).

Pathology. Grossly, the lesion is cystic, varying in size and configuration, and has a delicate capsule with a white, pearly sheen, containing varying amounts of a waxy, glistening, white or creamy, granular appearing material. This material is sometimes arranged in an onion skin fashion and is formed by continuous exfoliation from the epithelial lining of the cyst.

Histology. Cholesteatomas are made up of a limiting membrane that has all the layers of the normal epidermis; the basal cells, prickle cells, granulosa layers, and the outer covering of keratin or corneum layer. The membrane may vary from several layers in thickness to an irregular rete peg type architecture extending into the underlying fibrous tissue. Desquamated keratin forms the contents of the lesion.

Treatment. Ideally, there should be complete removal of the lesion, particularly the squamous epithelial lining, or recurrence is a good possibility. The restoration of the normal anatomy of the middle ear cleft with repair of drum destruction is desirable for the best prognosis.

The histology of cholesteatomas is certainly not dramatic, but the pathologist should not regard the diagnosis lightly, because of the serious complications that can ensue from this lesion. He and the otologist should require the presence of the definite histologic characteristics before making a diagnosis of cholesteatoma.

Cholesterol granuloma is a histologic term utilized to describe a tissue inflammatory reaction in the presence of cholesterol crystals (Linde). A serious mistake is to consider cholesterol granuloma as being synonymous with cholesteatoma. Although both can occur simultaneously, the cholesterol granuloma means hemorrhage has occurred in the area of involvement, usually the middle ear cleft. This can occur behind an intact drum, the so-called blue drum, as an isolated finding, or in association with any other middle ear disease, particularly otitis media. The gross appearance is that of a brown to green to yellow "fatty" or "greasy" tissue which may reveal glistening cholesterol crystals. The large lesion may cause bone destruction. The structure is that of a chronic inflammation characterized by numerous foreign body, multinucleated giant cells intermixed with varying numbers of rhomboid-shaped empty spaces (fig. 324). The cholesterol is dissolved in the histotechnical process. The cholesterol crystals are felt to be due to collections of the lipid from the cell membrane of destroyed

Figure 324
CHOLESTEATOMA GRANULOMA
This represents a cholesterol granuloma with the numerous cholesterol clefts due to accumulation of lipoid material. This reaction follows a hemorrhage. X63.

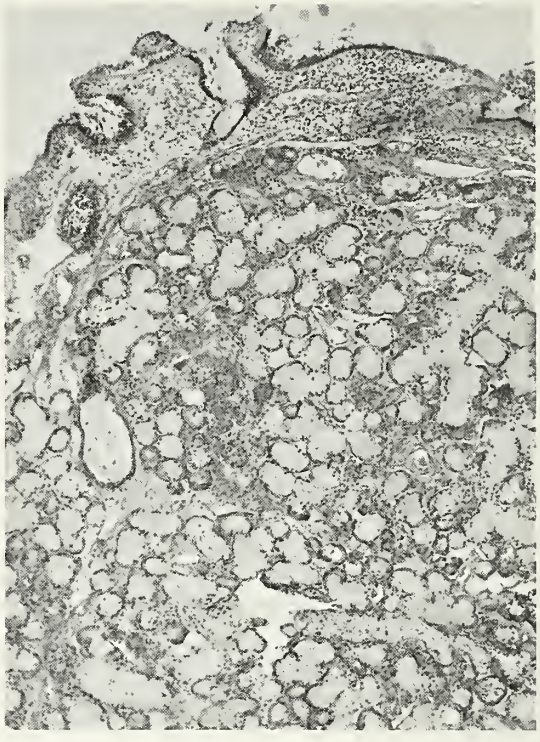

Figure 325
CHORISTOMA
This represents an isolated tumor of normal mucoserous salivary gland found in the middle ear. It qualifies as a choristoma. X63.

red blood cells. Treatment consists of operative removal of the inflammatory material, as well as correcting any condition contributing to the otitis media.

TERATOMAS, HAMARTOMAS, AND CHORISTOMAS

The AFIP-OTR material contains 10 teratomas (dermoid), 3 hamartomas, and 2 choristomas involving the middle and inner ear (Table 25). The choristomas appear to be mainly ectopic salivary gland tissue in the middle ear (Quaranta et al.) (fig. 325). These tetragenous tumors, particularly teratomas, may cause destructive symptoms and signs, but local assured complete removal offers a good prognosis. Hamartomas are discussed in the section on Tumors of the Upper Respiratory Tract.

ADDITIONAL TUMOR-LIKE OR QUESTIONABLE NEOPLASTIC LESIONS OF THE MIDDLE EAR

Temporal bone encephaloceles are tumor-like masses of cerebral tissue found in the middle ear and felt to be due to either infection, trauma, or congenital disruption of the integrity of the tegmen (bony roof of the middle ear). X-ray study may not visualize a bony defect (Kamerer and Caparosa). There are

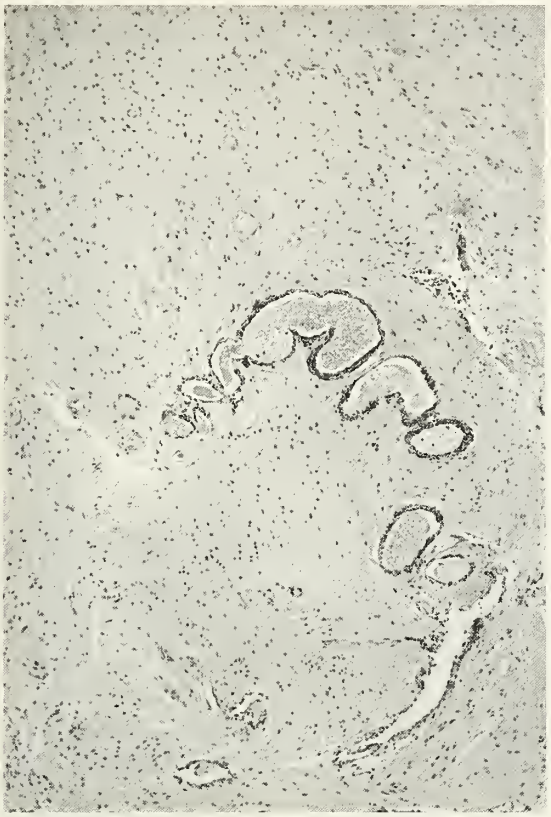

Figure 326
ECTOPIC CENTRAL NERVOUS SYSTEM TISSUE
A mass was found in the right middle ear behind an intact drum in a 50 year old adult with a lifelong history of a right conduction hearing loss. There was no connection with the cranial cavity, as the tegmen was intact. This central nervous tissue with glandular inclusions of middle ear mucosa was considered an ectopic central nervous tissue deposit in the middle ear. X63.

several cases in the AFIP-OTR material of apparent ectopic central nervous system tissue (glioma) deposited in the middle ear cleft (fig. 326), so diagnosed because of the failure to identify any connection with the cranial cavity. The histology suggested a brainlike appearance, but without definite identification of neurons. Porencephalic cysts are fluid-filled, apparently leptomeningeal-lined cysts that can have a delayed presentation in the middle ear or external canal following trauma (Konrad et al.).

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NEOPLASMS OF THE MIDDLE EAR

JUGULOTYMPANIC PARAGANGLIOMA

SYNONYMS AND RELATED TERMS: Glomus jugular tumor; glomus tympanicum; non-chromaffin paraganglioma; chemodectoma.

Definition. The jugulotympanic paraganglioma is a true neoplasm of varying aggressiveness, apparently originating from extra-adrenal paraganglia of the temporal bone area and essentially retaining the histologic appearances of the normal paraganglia.

Incidence and Sites of Tumor. Of the approximately 250 benign and malignant primary neoplasms of the middle ear space and its surrounding tissue that are listed in the AFIP-OTR, one third are paragangliomas. This neoplasm is the most common of this anatomic area. Of the AFIP-OTR cases, 85 percent arose from the jugular bulb area, 12 percent in the middle ear space, and the remainder in the external ear canal, apparently from paraganglia associated with Arnold's nerve (fig. 327). A rare case was recorded as arising in the para-eustachian tube tissue, perhaps from paraganglia of the lesser petrosal nerve. In spite of the close approximation of the intravagal paraganglia in the ganglion nodosa of the vagal nerve, paragangliomas of this structure are not included as part of the jugulotympanic paragangliomas. Symptoms of the intravagal paragangliomas center around an upper neck mass and can occasionally involve the middle ear proper with symptoms indistinguishable from the jugulotympanic paraganglioma.

Clinical and Gross. Three out of four patients are female (Alford and Guilford). Ages of patients at diagnosis varied from 13 to 85 years, with the majority in the 40 to 60 age group (mean average 50 years). Symptom duration prior to diagnosis varied from several weeks to decades, with an average of 3.3 years (Spector et al.). Familial clusters and occurrence at multiple sites, such as the opposite ear, carotid, and aortic paraganglia are recorded (Resler et al.). There is no established relationship with preceding middle ear infection. The predominant symptom is conductive hearing loss, but tinnitus, facial nerve palsies, otic discharge, pain, vertigo, and hemorrhage may present. Endocrine activity of a pheochromocytoma or carcinoid type is described (Farrior et al.). Physical examination most often reveals a polypoid mass presenting in the external ear canal or behind a bulging drum. It may vary from a small 2 to 3 mm red mass on the promontory to a friable, infiltrative hemorrhagic, beefy tumor occupying the entire middle ear and beyond. Profuse bleeding on manipulation has been a constant observation and lack of bleeding in a traumatized middle ear tumor should cause doubt as to the diagnosis of paraganglioma. Radiography may reveal a soft tissue mass, a bony sclerosis, or erosion. Angiography yields a characteristic vascular stain.

Microscopic. The diagnostic histologic finding is the cell nest or "zellballen" pattern of paraganglia in general. The nests, varying from several to as many as 20 or 30 cells, are surrounded by variable bands of fibrous tissue containing usually prominent vascular spaces. The individual tumor cell is best described as epithelioid, with no attempt at a glandular or alveolar arrangement. Cytoplasm of varying amounts is noted and nuclei are generally uniform, but may be hyperchro-

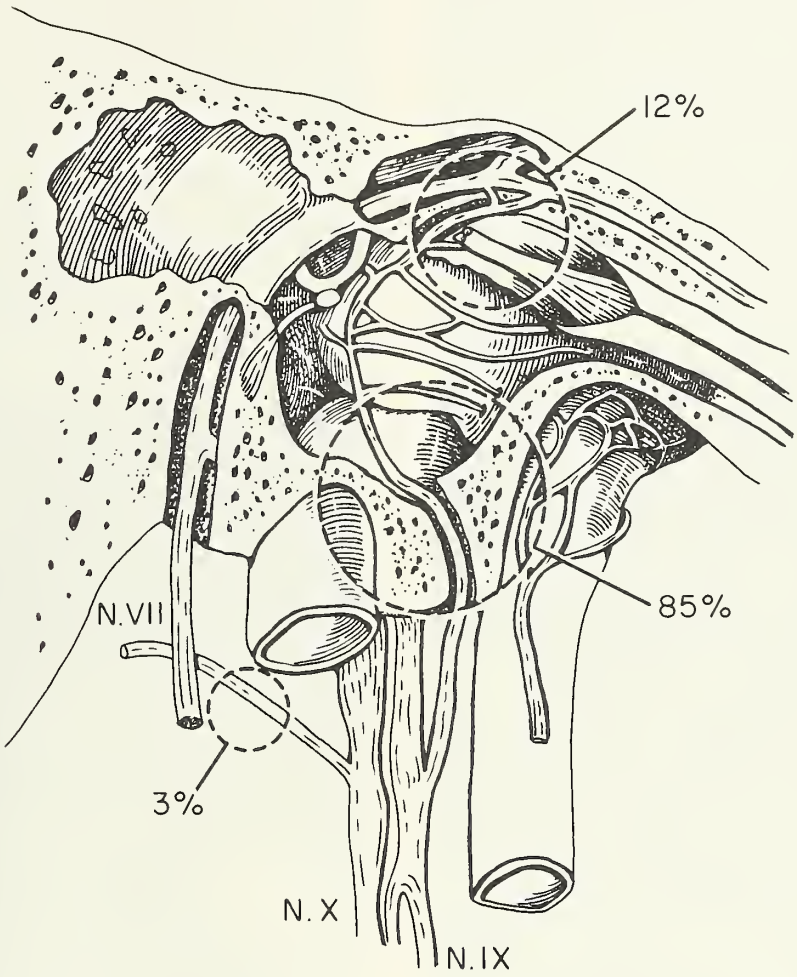

Figure 327
JUGULOTYMPANIC PARAGANGLIOMA
This schematic presentation indicates the anatomic location of 90 cases of jugulotympanic (temporal bone) paragangliomas in the AFIP-OTR (1940 through 1975). (Adaption of drawing courtesy of Dr. F.G. Zak and Dr. W. Lawson.)

matic or pale with prominent nucleoli (fig. 328). Special histochemical studies demonstrate no specific reactions in tumor cells, although a reticulum stain may help to outline the cell nest pattern, particularly where anaplasia is prominent (fig. 329).

Electron microscopic studies (Glenner and Grimley) and formalin induced fluorescence (DeLellis and Roth) reveal neurosecretory granules and norepinephrine production (fig. 330), supporting derivation from the paraganglia. Sustentacular cells and nerve axons are not readily demonstrated in the neoplasm. Occasionally, the jugulotympanic paraganglioma may demonstrate anaplasia with hyperchromatic nuclei, but rarely a mitotic figure (fig. 331).

Differential Diagnosis. Clinically and grossly, other entities, such as inflammation, cholesteatoma, and various neoplasms, must be ruled out. In the AFIP-OTR, meningioma, adenoma of the middle ear, poorly differentiated carcinoma, and vascular tumors are most commonly confused histologically with the jugulotympanic paraganglioma. Glenner and Grimley discuss the hemangiopericytoma, carcinoid, alveolar soft part sarcoma, and metastatic thyroid carcinoma as difficult

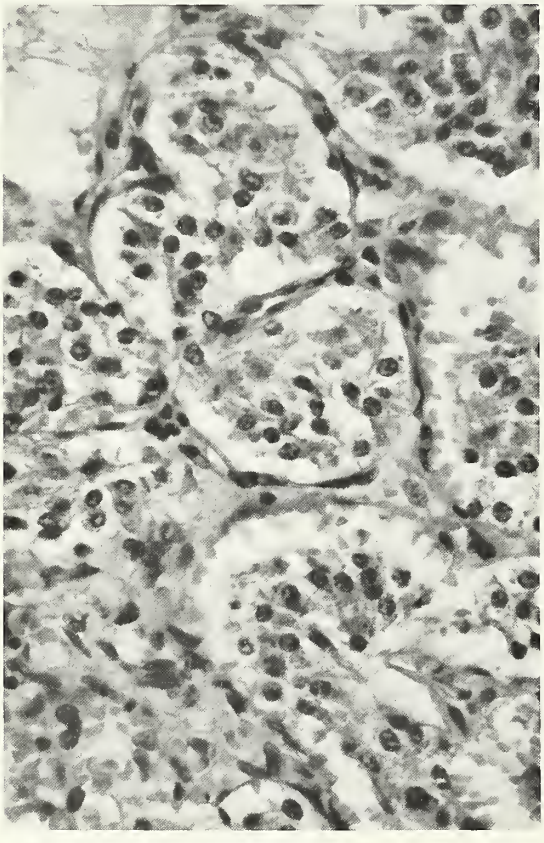

Figure 328
JUGULOTYMPANIC PARAGANGLIOMA
This reveals the epithelioid character of the neuroectodermal derived neoplastic cells, as well as the absence of a definite glandular or alveolar tumor cell arrangement. X400.

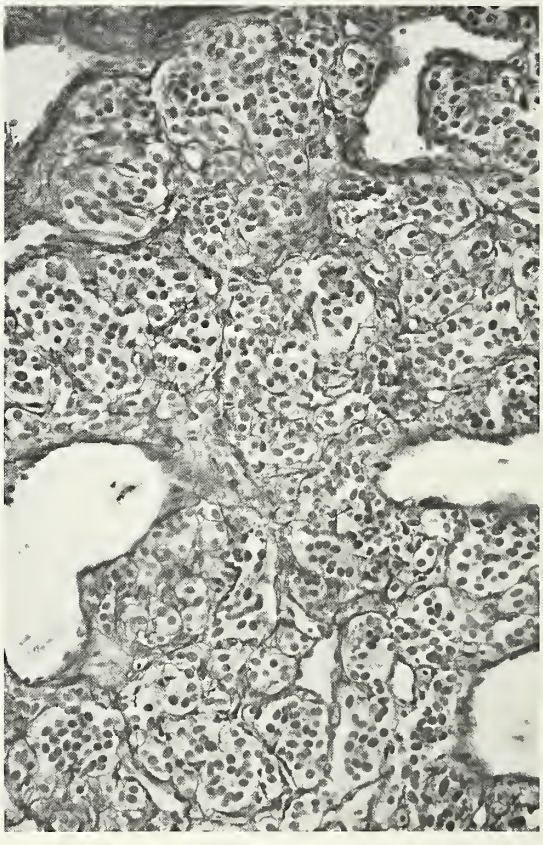

Figure 329
JUGULOTYMPANIC PARAGANGLIOMA
In this reticulum stain on the paraganglioma, the cell nest pattern is emphasized by strands of reticulum surrounding the nest, but not separating the tumor cells. X160.

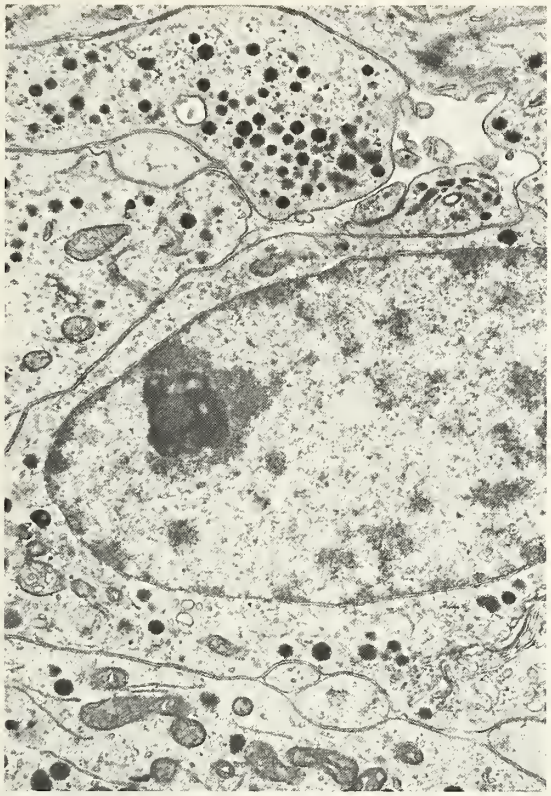

Figure 330
JUGULOTYMPANIC PARAGANGLIOMA
An electron microscopic view of a jugulotympanic paraganglioma supports the neuroectoderm features by the presence of neurosecretory-like granules. X9000.

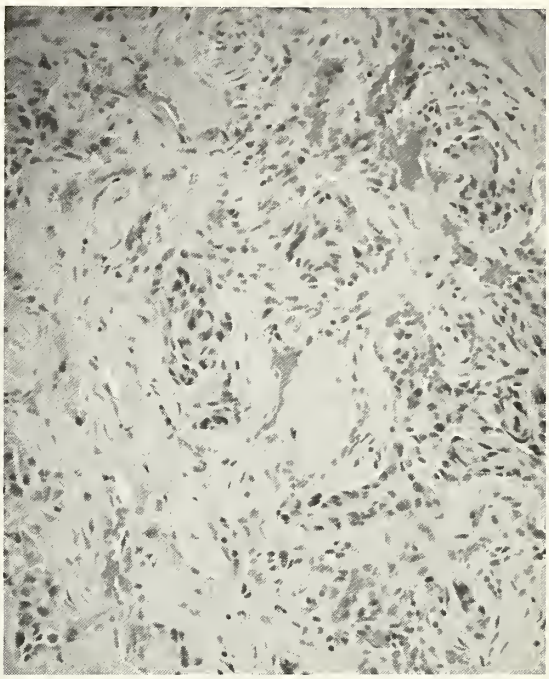

Figure 331
JUGULOTYMPANIC PARAGANGLIOMA
Occasionally the cell nest pattern is not well delineated in a jugulotympanic paraganglioma and the histology appears anaplastic. A reticulum stain may serve to bring out the cell nest pattern (fig. 329). X160.

differential diagnoses. Manipulation of the tumor tissue during biopsy and reactive changes in the neoplasm may serve to further obscure the true histologic diagnosis.

Natural History. The usual long-term clinical symptomatology is characteristic of slow growth and, even though there is the occasional confinement of the tumor to the middle ear, the more common behavior is the infiltration of adjacent bone. There is a reported 2 percent incidence of distant metastasis and a 6 percent incidence of concomitant paragangliomas occurring at other paraganglia sites (Alford and Guilford). An important observation in the study of AFIP-OTR material is the lack of correlation of histology with clinical behavior. The most uniform microscopic pattern of the jugulotympanic paraganglioma may be accompanied by marked spread and aggressive local behavior in spite of accepted therapy, while the more cytologically anaplastic paragangliomas may remain quite localized. Recurrence rates are reported in one-third to one-half of treated cases and mortality figures are stated at around 17 percent (Rosenwasser). Death usually results from local spread of the tumor into adjacent vital cavities, mainly the cranial cavity.

Treatment. Removal will usually suffice for small localized lesions; however, preoperative or postoperative radiation with surgery has offered a better outlook. Radiation therapy

alone has occasionally been curative or prevented further aggressive behavior with inoperative or recurrent tumors. Embolic therapy has also had its advocates.

EXTRA-ADRENAL PARAGANGLIOMAS

Tumors arising from paraganglionic tissues, which are intrinsic to the upper respiratory tract and paratemporal bone area, are far fewer than those originating in the major paraganglia of the head and neck. In some instances, such as the nasal cavity and nasopharynx, the reporting of the presence of a paraganglioma has preceded the identification of a normal paraganglia.

Intravagal paraganglioma has a relatively infrequent occurrence, estimated from a survey of medical literature figures to comprise 2 percent of all head and neck paragangliomas. Of the 37 cases of vagal paraganglioma found in the literature, 26 occurred in women, with the patients' ages ranging from 18 to 65 years (average 37 years) (Glenner and Grimley).

They arise most commonly near the jugular foramen attached to the emerging vagal nerve and usually involve the ganglion nodosum. The tumor presents high in the anterolateral aspects of the neck beneath the ear, and a leading symptom with intravagal paraganglioma is hoarseness and difficulty in swallowing. There is also the possibility of extension into the temporal bone, mimicking the symptoms and signs of the jugulotympanic paraganglioma (Hirsch et al.). The histology and the therapeutic approach is essentially that of the jugulotympanic ganglioma.

Nose and Nasopharynx. Lawson has recorded 16 patients with paragangliomas arising in the nose and nasopharynx, presumably from undescribed paraganglionic tissue present there. Secondary extension from jugular body paragangliomas must be excluded.

Among the primary cases, the age range was from 8 to 92 years (mean 45 years). Females outnumbered males in a ratio of 3 to 1. Additional references to nasal cavity and nasopharyngeal paragangliomas are found in articles by Himelfarb and associates and Schuller and Lucas.

The presenting complaints include nasal obstruction, epistaxis, sinusitis, and otologic symptoms from eustachian tube obstruction. Radiography may reveal a soft tissue mass, a bony sclerosis, or erosion. Angiography yields a characteristic vascular stain which can be differentiated from that of juvenile angiofibroma.

While locally aggressive, none of the tumors revealed metastases.

Excision appears to be the treatment of choice. These tumors appear generally to follow a protracted clinical course despite lack or failure of treatment.

Larynx. In contrast to the apparent sparsity of paraganglionic tissue in the nose and paranasal sinuses, the larynx is relatively rich in such tissue (Lawson and Zak).

Twenty-seven cases of laryngeal paragangliomas are reported in the medical literature (Hordijk et al.), and an additional six patients are listed in the AFIP-OTR. The ages ranged from 14 to 86 years, with 13 of 17 reported patients being male (Wetmore et al.).

There are four normal paraganglia identified in the larynx (fig. 332), one each usually in the area of the entrance to the bilateral superior and inferior laryngeal vessels and nerves into the larynx proper. Although the paragangliomas can arise from any area of the larynx, the majority arose from the supraglottic area, especially in the aryepiglottic fold.

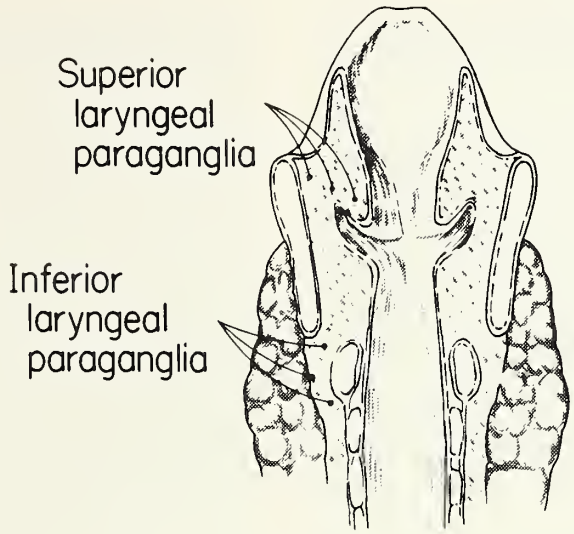

Figure 332
NORMAL PARAGANGLIA
This schematic drawing indicates the areas of normal paraganglia in the larynx. There should be four bodies, with one each at the entrance of the bilateral superior and inferior nerves and vessels into the larynx.

Lawson has reviewed 32 laryngeal paragangliomas. Thirty of the tumors arose from the superior bodies of paraganglia. These presented as smooth, seemingly cystic, to fleshy, beefy, mucosal-covered swellings of the supraglottic larynx, varying from 5 mm to 6 cm in diameter, and extended unilaterally from the aryepiglottic fold to the ventricle. In two instances, the tumor arose from the inferior bodies and appeared as a subglottic mass. The right side has been involved twice as often as the left. Hoarseness, dysphagia, neck mass, and pain, listed in their order of frequency, were the principal presenting symptoms. Histology will imitate the typical head and neck paragangliomas with the same diagnostic differential.

There may be a confusing differential problem with adenocarcinoma of the larynx, as discussed on page 101. Laryngeal adenocarcinoma may imitate somewhat the "cell nest" pattern of the paraganglioma. A microscopic search of the adenocarcinoma will usually reveal definite neoplastic glandular structures, sometimes even mucus production, findings incompatible with the diagnosis of a paraganglioma. Confusingly, these adenocarcinomas of the larynx will show intracellularly the ultrastructural membrane-bound bodies considered consistent with neural crest derived neoplasms. This has led to the designation of the adenocarcinoma as a carcinoid tumor of the larynx. These laryngeal adenocarcinomas have a more malignant course, with a higher rate of metastasis than the laryngeal paraganglioma. The clinical behavior of the laryngeal paraganglioma has been generally localized to the organ and treatment is directed at an assured complete removal. Lawson reported metastasis in 6 of 32 patients. Liew and associates reported a patient with tracheal paraganglioma.

MENINGIOMA OF THE TEMPORAL BONE

Meningiomas involving the temporal bone are no different in clinical behavior or histologic variation than those confined to the intracranial space, but it is not commonly recognized that they can originate independently of intracranial origin in the middle ear, internal auditory canal, and jugular fossa (fig. 333). However, there are still the rare meningiomas of these extracranial areas that are not primary extracranial or extraspinal meningiomas, but, rather, extensions of intracranial meningiomas.

Incidence and Sites of Tumor. Nager reports meningiomas as representing 18 to 19 percent of intracranial neoplasms, with 6 to 7 percent of all intracranial meningiomas arising from the surface of the petrous bone, thus presenting the possibility of invasion of the temporal bone itself. The English and French literature reports 19 cases of primary intratympanic meningiomas (Salama and Stafford), while the AFIP-OTR files contain 17 patients with meningiomas apparently also arising in the middle ear cleft de novo.

Clinical. Those meningiomas arising from the surface of the petrous bone will reveal symptoms associated with middle and

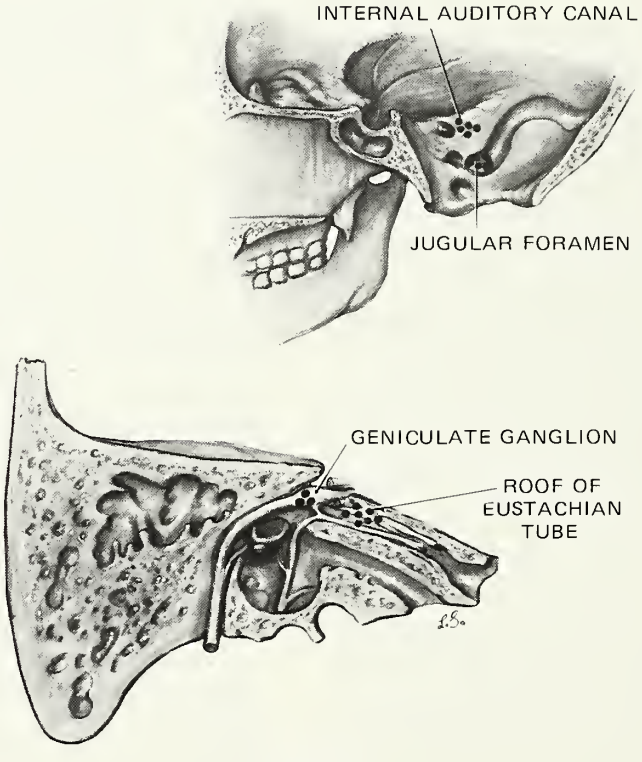

Figure 333
MENINGIOMA
These drawings represent sites of primary extracranial meningiomas involving the temporal bone area. (Fig. 54 from Nager, G.T. Meningiomas Involving the Temporal Bone. Springfield, IL: Charles C. Thomas, 1964.)

posterior cranial fossa tumors. When the internal auditory canal is involved, the clinical presentation will be indistinguishable from the acoustic neurilemoma of that anatomic area. Once the tumor has gained access to or originates from the middle ear, symptoms of chronic tympanomastoiditis or an acute otitis media develop, and tumor tissue appears in a form suggesting granulation tissue or polyps, or is manifested by hyperemia and infiltration of the tympanic membrane or mucoperiosteum of the middle ear. In the course of the tumor growth, certain structures of the middle ear, such as the facial nerve and chorda tympani nerve, may become involved and the conduction of sound may become affected. Radiographic examination may reveal destruction and erosion of bone with, occasionally, associated adjacent bony increased density or sclerosis. Temporal bone meningiomas are recorded in increased frequency in patients with von Recklinghausen's neurofibromatosis (Nager).

Pathogenesis. Meningiomas may arise from dural fibroblasts and pial cells, but most stem from arachnoid cells, particularly those forming the arachnoid villi. These latter are a part of the meninges regarded as neuroectodermal in origin (Rubinstein). Arachnoid cell clusters and/or granulations are encountered within the internal acoustic meatus and jugular foramen, at the geniculate ganglion, and the roof of the eustachian tube and the sulcus of the greater petrosal nerve. Their location in these sites in the temporal bone would account for the origin of the meningioma in these same areas.

Gross. Although meningiomas are described as characteristically well circumscribed, globular, or lobulated tumors well demarcated from the brain (Rubinstein) in their intracranial location, in temporal bone meningiomas there is a tendency to infiltrate the bone with invasion of the mastoid cavity and pneumatic cells, external ear canal, jugular fossa, carotid canal, and even into the nasopharyngeal area. Occasionally the membranous labyrinth may be involved. The tumor is usually firm, tough, gray or pink-gray, with a faintly lobular pattern and granular consistency. During temporal bone surgery, the lack of profuse hemorrhage on manipulation suggests a neoplastic process other than the jugulotympanic paraganglioma, which is usually the diagnosis clinically suspected. Occasional gritty foci formed of psammoma bodies may be encountered. Nager, in a review of the literature, recorded cervical lymph node metastasis in 2 of 30 patients with temporal bone meningiomas. The metastasis occurred prior to surgery and had a benign histologic structure identical to the primary neoplasm.

Microscopic. Although the microscopic appearance of meningiomas is highly variable and the tumors may be separated into the meningotheliomatous, fibroblastic, transitional, psammomatous, and angioblastic, they are all manifestations of the meningothelial arachnoid cell, and there is no particular prognostic significance attached to the histologic groupings. The most commonly encountered histologic form involving the temporal bone is the meningothelial type (fig. 334), where the tumor cell suggests a plump bipolar morphology, but with poorly defined cell membranes and regular round and oval nuclei. The tumor cells are arranged in strands and nests displaying a formation of whorls in which the cells are wrapped around one another, suggesting a cut onion. Variable amounts of fibrous tissue divide the tumor lobules and may proliferate and blend with the meningothelial neoplastic cell to form the so-called transitional or mixed type meningioma. Although frequent in intra-

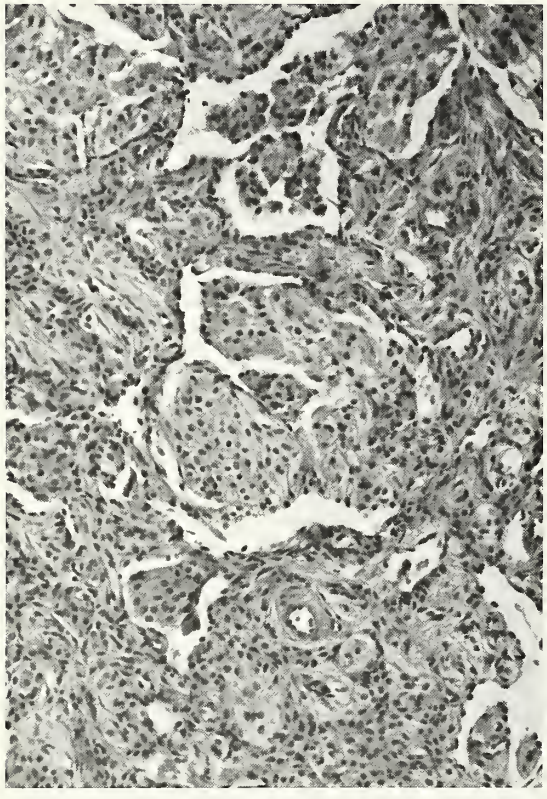

Figure 334
MENINGIOMA
This view of a meningotheliomatous intratympanic meningioma emphasizes the whorl-like pattern. X160.

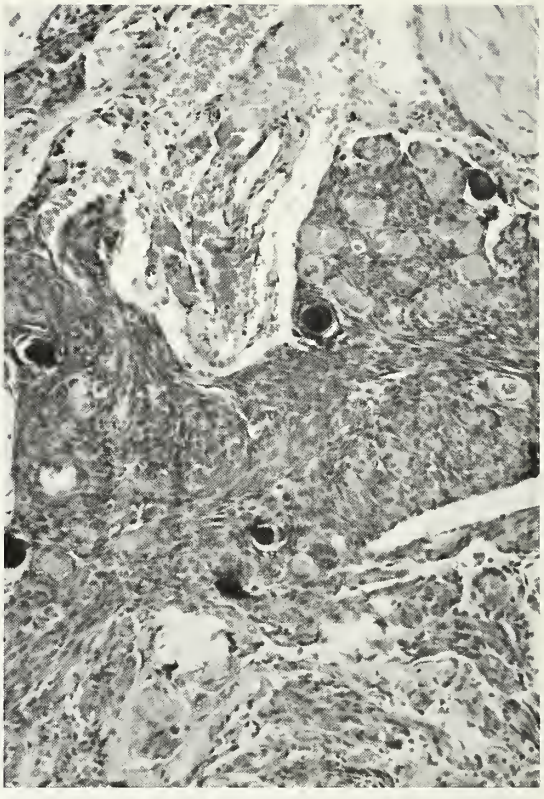

Figure 335
MENINGIOMA
This psammomatous meningioma of the intratympanic area reveals the round and spheroid calcified bodies (psammoma bodies) that make the diagnosis of meningioma most reliable. X160.

cranial meningiomas, psammoma bodies (which are spherical formations of concentric lamina with calcium salts deposition) are relatively rare in temporal bone meningiomas (fig. 335). Their presence has led to the designation of the psammomatous type meningioma.

The fibroblastic type meningioma is a tumor of distinctive fibrocystic-looking cells, which may show a tendency toward whorls or palisading with even an occasional psammoma body. Areas may contain small clusters of the typical meningothelial cells. This type, and the so-called angioblastic meningioma, a form characterized by a multitude of contained blood spaces, rarely involve the temporal bone. The malignant or sarcomatous form of meningioma has not been recorded with certainty in the temporal bone.

Treatment and Prognosis. The treatment is surgical with no reported response to irradiation or chemotherapy. Although the survival following surgery for intracranial meningiomas is favorable (average survival range is 12 to 15 years) (Rubinstein), In Nager's review of 30 patients from the literature, only 2 had survived extension of the intracranial neoplasm to the temporal bone. In the 10 patients with primary middle ear cleft

meningioma with adequate follow-up information, from the AFIP-OTR, there was only 1 death during a mean follow-up time of seven years. This marked difference of survival appears related to the origin from the middle ear with comparatively easy surgical access, in the AFIP-OTR material, while the cases in Nager's series were essentially of origin from the petrous surface of the temporal bone with invasive spread into the temporal bone.

Differential Diagnosis. Meningiomas involving the middle ear cleft may be thought clinically to be jugulotympanic paragangliomas, and those in the cerebello-pontine angle or internal auditory canal will be diagnosed preoperatively as acoustic neurilemomas. Histologic examination will usually correct the diagnosis. Resemblance between meningiomas and paragangliomas can be confusing (Maniglia). Utilizing a reticulum stain (fig. 336), there were positive fibers throughout the meningeal cell groups, in contrast to the paraganglioma where the cell nest is free of reticulum fibers (fig. 329). Clinically, if the neoplasm does not bleed profusely on manipulation, the chance of its being a paraganglioma is greatly decreased.

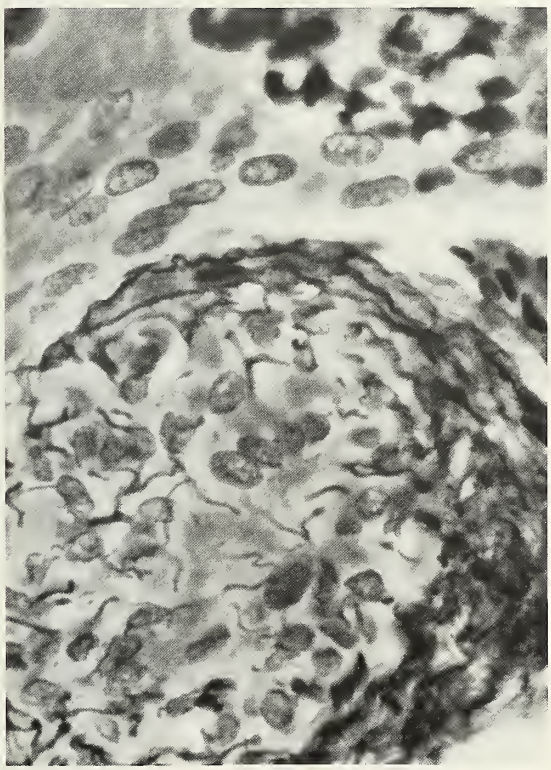

Figure 336
MENINGIOMA
Quite often the pathologist will be undecided upon the diagnosis of meningioma versus jugulotympanic paraganglioma. The author (VJH) has been able to demonstrate reticulum intraneoplastically, whereas this is not seen in the cell nest of the paraganglioma (see figure 329). X320.

EXTRACRANIAL MENINGIOMA OF THE UPPER RESPIRATORY TRACT

Although one may feel that most meningiomas presenting in the sinonasal tract have their origin in the anterior cranial fossa, especially over the cribriform plate, orbital cavity, or the medial portion of the sphenoid ridge, in Wolman and Path's series of 375 intracranial meningiomas, only 2 involved the nasal and sinus air passages.

There were 24 patients with extracranial origin meningiomas arising in the paranasal sinuses (Sadar et al.), all of which were felt originally to have a neoplasm of the area, but were not suspected clinically of harboring a meningioma. Central nervous system vestiges and occasional arachnoidal nests on the nasal side of the bony plate of the cribriform apparatus are potential sources of ectopic meningiomas.

Other literature reports indicate primary extracranial meningiomas of the external nose, nasal cavity, and external ear (Lopez et al.). The AFIP-OTR lists the nasal cavity, nasopharynx, major salivary glands, and upper neck as additional sites. The rare angiomatous and fibrous meningioma may occur

and, possibly, a malignant sarcomatous variety (Sadar et al.). The clinical behavior is for the most part a localized aggression and, although occasionally persistent, assured complete removal should afford a good prognosis.

By 1973, five primary extracranial parapharyngeal meningiomas had been reported in the English literature (Whicker et al.). Lesions originating within the jugular foramen and parapharyngeal extension from an intracranial meningioma must always be considered. Arachnoid cells on the deep surface of the facial nerve or extracranial infiltration are held accountable for those meningiomas involving the infratemporal region.

ADENOMA OF THE MIDDLE EAR

This is a controversial and scantily documented neoplasm occurring in the middle ear and mastoid spaces, apparently arising from the middle ear mucosa and particularly characterized by a nondestructive and nonaggressive clinical and radiologic behavior in relationship to the surrounding middle ear cleft bony confines (Hyams and Michaels).

Incidence. The middle ear adenoma is more common than the English medical literature suggests. A review of middle ear and mastoid tumors from the AFIP-OTR, up to the present time, revealed over 100 cases of adenomatous neoplasms conforming to the above definition. They had been variously diagnosed as adenocarcinomas, ceruminal adenomas, and jugulotympanic paragangliomas.

Clinical. A detailed investigation of 20 patients with the diagnosis of middle ear adenoma (Hyams and Michaels) revealed an even sex distribution and an age range from 14 to 80 years, with three-quarters of the cases occurring in the second through fourth decades. The chief complaint was unilateral increasing conductive deafness with a rare manifestation of fullness and tinnitus. Pain, facial weakness, and otic discharge were mainly absent. The ear examination revealed a normal external auditory canal with an intact drum in 15 of the 20 patients. In three patients, tumor did present through a drum perforation, but for the most part the neoplasm was confined to the middle ear, with occasional extension into the mastoid spaces. There was no clinical or radiographic evidence of bony destruction or invasion by tumor. In later patients studied from AFIP-OTR material, there were several who did present facial nerve weakness on the involved side, but in most there was drum perforation and microscopic evidence that supported the diagnosis of a cholesteatoma that could have been the cause of the facial nerve involvement. Also in the AFIP-OTR material there is histologic superficial bone erosion in the exceptional case. Usually this erosion was not detected by radiographic study. At exploration, the tumor can be a small or large mass anywhere in the middle ear spaces and involve any middle ear structure, such as ossicles and the chorda tympani nerve. It always is attached to the mucosal surface at some point. The mastoid spaces and, less frequently, the eustachian tube may be involved. A rare patient in the AFIP-OTR and the series reported by Jahrsdoerfer and associates demonstrated growth from the middle ear through an intact drum into the external auditory canal. The tumor varies grossly from white, gray, or red-brown, and is gritty, fibrous, and rubbery, with comparatively little bleeding on manipulation. This observation is frequently the first indication to the surgeon that he is probably not deal-

ing with a jugulotympanic paraganglioma (glomus jugulare tumor). Some surgeons noted the ease with which the tumor peeled from the surrounding middle ear walls. Occasionally, the ossicles are found to be entrapped in the tumor mass and may show destructive changes.

Microscopic. Demarcation or encapsulation are not demonstrated in the usual fragmented surgical specimen. An adenomatous pattern is always demonstrated; however, portions, and occasionally a major part, of the structure consist of incohesive sheets of irregular tumor cells (figs. 337-339). Essentially cuboidal or cylindrical cells form the single layered glandular structures with a tendency to assume the "back-to-back" configuration. Another pattern seen is a trabecular architectural arrangement of one to three cell thickness. No myoepithelial cells are detected. The individual cell, whether forming glands or sheets, is round, ovoid, or cuboidal and appears similar to the middle ear mucosal cell. The cytoplasm varies in amount, but has an eosinophilic, finely powered appearance, with occasional vacuoles and argyrophilic positive, but argentaffin negative, basal granules (Grimelius, Fontana stains). The nuclei are spheroidal to oval with dense, diffuse chromatin, occasional faint

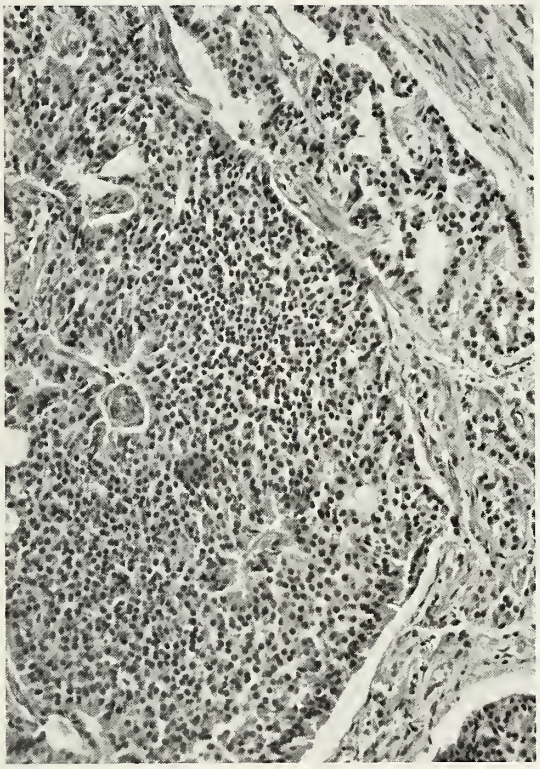

Figure 337
(Figures 337 and 338 are from the same patient)
ADENOMA
This represents the typical histology of adenoma of the middle ear mucosa, with areas of sheets of small uniform cells alternating with foci of definite glandular structures. X63.

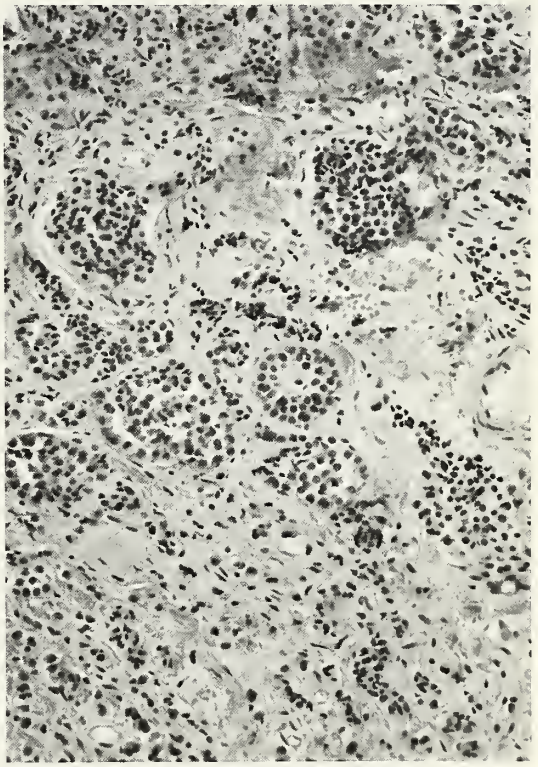

Figure 338
ADENOMA
The resemblance to a paraganglioma histologically is real, but the areas of glandular formation in the previous illustration rule out this latter differential consideration. X160.

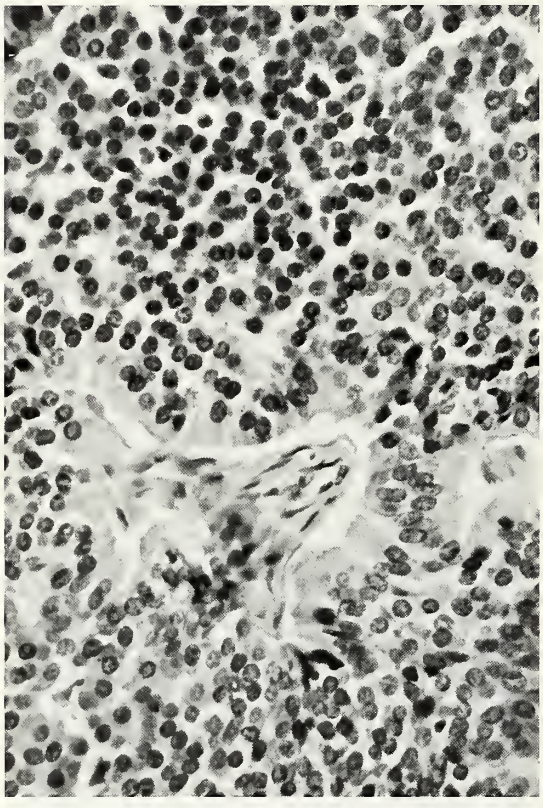

Figure 339
ADENOMA
This magnification supports the uniformity of the neoplastic cells and the formation of a glandular architecture. Occasionally, mucin will be detected in the glandular lumen. X160.

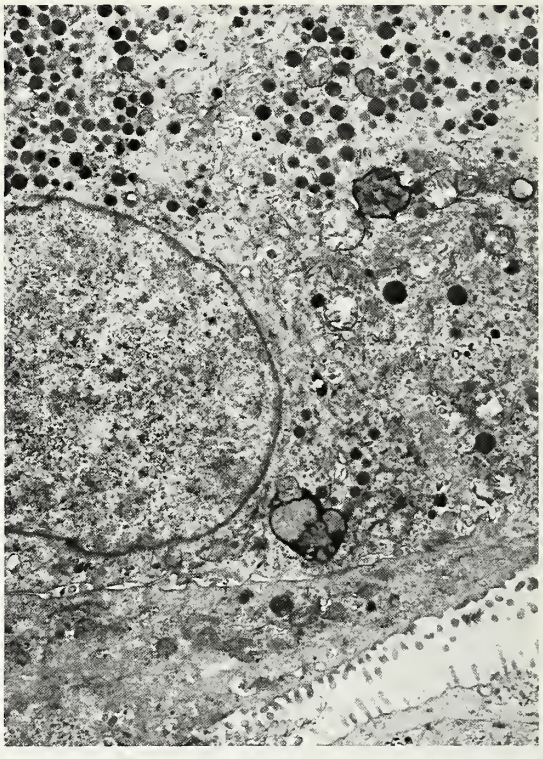

Figure 340
ADENOMA
The electron microscopic view shows two types of cells. One an apparent lumenal cell with prominent microvilli; the other cell type is characterized by numerous secretory granules. Desmosomes are prominent between all cell types. A variety of cytoplasmic organelles are present. X5000.

nucleolus, and are quite often eccentric within the cell. In the sheetlike arrangements of tumor cells, there is a resemblance to a plasma cell infiltrate. Mitosis is extremely rare. An isolated larger cell, two to four times larger than the other tumors cells, can be identified occasionally. Mucicarmine positive material may be present in a gland lumen and on the cell apical surfaces, but no intracytoplasmic mucin is demonstrated. Iron stains are negative. Fragments of neoplasm in patients with a drum perforation may be overlaid by keratinizing stratified squamous epithelium. Such findings suggest a concomitant cholesteatoma. Variable amounts of vascular myxomatous to fibrous stroma is seen. There are also variable sized foci of cells with pyknotic nuclei and scant contracted cytoplasm. This micromorphology suggests degenerating cells or, possibly, operative "crush artifact." Sometimes a decision is quite difficult as to whether this histologic finding represents significant anaplasia. Necrosis is usually absent. Three cases in the AFIP-OTR material revealed perineural space invasion, but there was no evidence of aggressive destruction or metastatic behavior even on long-term followup.

Ultrastructural studies (fig. 340) confirm the basic acinar organization of the neoplasm

(Riches and Johnston) with cuboidal to columnar cells nesting on a distinct basal lamina. Microvilli are present on the apical surfaces of the glandular cells. Desmosomes are located along the lateral and basal aspects of the plasma membranes and tight junctions are usually present adjacent to the gland lumens. A variety of cytoplasmic organelles are present. Distinct membrane limited dense granules (greater than 300 nm in diameter) (? neurosecretory granules) is a most prominent feature in some deep cells, while the surface lining cells with the microvilli will be granule free. Light and dark cells are described based upon the relative density of the cytoplasm. Perinuclear microfilaments are seen, but are not distinctive of a myoepithelial cell.

Histogenesis. The epithelium of the middle ear has a propensity in inflammation for metaplasia to a ciliated respiratory type with accompanying secretory cells. This supports the idea that the mucosa is capable of neoplastic proliferation. Some cases, microscopically, support the origin of the adenoma as a transition from mucosa to neoplasm (fig. 341). The ultrastructural features are similar to the normal middle ear mucosa and the large membrane bound granules are seen in some cells forming the normal middle mucosa (Lim). The exact nature of these granules remains unsolved, with suggestions that they are neurosecretory, enzymatic, or mucinous. Ectopic ceruminal glands in the middle ear cleft have never been noted in AFIP-OTR material nor described in the liter-

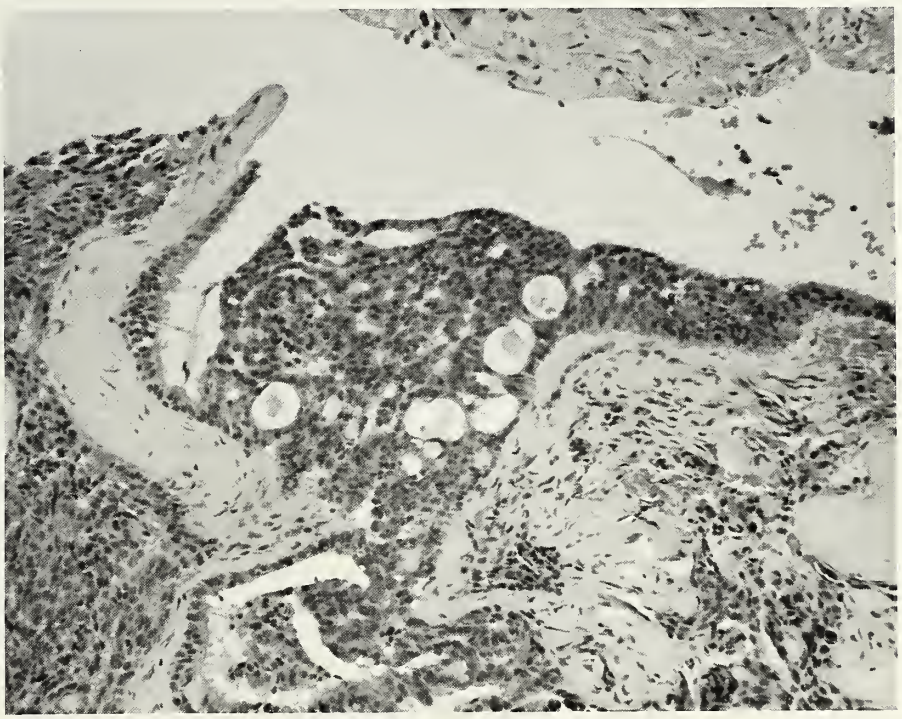

Figure 341
ADENOMA
Magnification shows the adenomatous middle ear neoplasm arising de novo from the middle mucosa. Note the adjacent ciliated normal middle ear mucosa. X160.

ature, so that the relationship suggested by Pallanch and colleagues to a ceruminal gland is not supported. The origin from paraganglia is not likely, because the adenomatous and sometimes mucinous features of the middle ear adenoma is incompatible with a paraganglioma histology.

Natural History, Treatment, and Prognosis. Removal is the treatment of choice. Jahrsdoerfer and associates suggested exploratory tympanotomy with simple excision of the tumor if the lesion is small and confined to the middle ear cleft. Radiotherapy has no place in the therapy of middle ear adenoma. In the 20 patients of the AFIP-OTR with adequate followup, all survived with local removal and there was only one recurrence seven years after initial removal. This patient underwent repeat removal and there was no recurrence 10 years after this second operation. This optimistic outlook is shared by those authors who accept the diagnosis of adenoma of the middle ear. Some have felt that some patients have local infiltration into surrounding bone, but not of sufficient intensity to be recognized radiologically or grossly. There is one interesting recent case from the AFIP-OTR that was diagnosed at 10 years of age as an adenoma of the middle ear and appropriately treated by local surgery; recently, however, a locally aggressive papillary adenocarcinoma has developed in the middle ear space.

Differential Diagnosis. If clinically and radiologically there is destruction of temporal bone osseous structures surrounding the middle ear, the neoplasm is obviously not an adenoma. The differential diagnosis should then lead possibly to a rare primary adenocarcinoma, metastasis from regional or distal sites (genitourinary tract, breast, external auditory canal, or nasopharynx), or another neoplastic entity, such as a jugulotympanic paraganglioma. There is the cystic chronic otitis media that could mistakenly be diagnosed as an adenoma. There is also the report of a primary carcinoid tumor of the ear (Inoue et al.; Murphy et al.).; however, there is no systemic manifestation in the patient with the middle ear adenoma that is consistent with the true functional carcinoid of the extratemporal bone sites. The clinical presentation, behavior, and structure of these published cases of the so-called carcinoid tumor of the middle ear supports the diagnosis of adenoma of the middle ear.

EPITHELIAL PAPILLOMA OF THE MIDDLE EAR

There were three patients in the AFIP-OTR data who presented with clinical symptoms and findings of adenoma of the middle ear, but the histology presented a papillomatous proliferation of middle ear mucosa. The cell type was a varying mixture of cytologically benign epidermoid and tall columnar epithelium resembling the so-called inverting papillomas of the sinonasal tract, even with the suggestion of "inversion" into an underlying fibrous stroma. The papillomas were limited to just the middle ear and responded to removal; however, one patient had several recurrences over a 10-year period.

ADENOCARCINOMA OF THE MIDDLE EAR

Until recently, the question of primary adenocarcinoma arising in the middle ear had been somewhat equivocal. The literature does contain many reports of adenocarcinoma involving the middle ear, but it is difficult in most of the published cases to rule out the possibility of metastasis from adja-

cent or distal anatomic areas or of the possibility of the occurrence of the adenoma of the middle ear reported in the previous pages. In Table 25 there are listed two patients with primary adenocarcinomas of the middle ear which resembled clinically as well as histologically (figs. 342, 343) an adenoid cystic carcinoma with distant metastasis. In spite of intensive surgical treatment, both patients died of their disease within two years of diagnosis.

In recent years, eight cases have come to the attention of AFIP-OTR of a slow-growing, locally destructive, but non-metastasizing neoplastic process involving the middle ear and temporal bone that we have termed papillary cystadenocarcinoma of the middle ear. The first cases seen, because of their clinical histology and involvement of the external auditory canal, led to the suggestion that this papillary cystadenomatous neoplasm was arising from the ceruminal glands of the external ear canal. However, additional patients have demonstrated only middle ear and temporal bone involvement isolated from any continuity with the external canal, which supported the origin from the middle ear spaces. The patients varied in age from the second to sixth decade, with no sex preference.

Histogenesis. Observations of this tumor entity supports origin from the middle ear mucosa. The majority of patients have confinement of the neoplasm to the middle ear

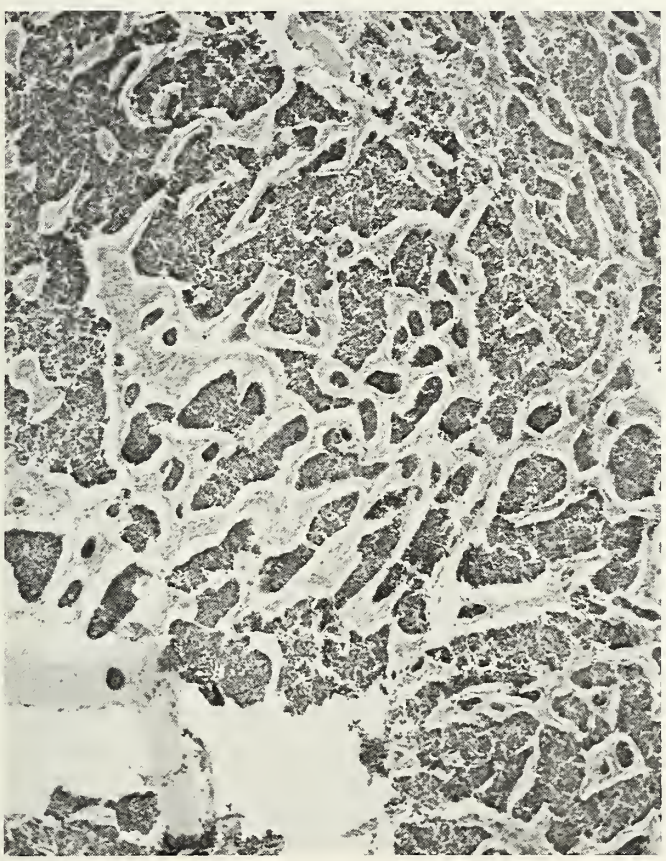

Figure 342
(Figures 342 and 343 are from the same patient)
ADENOCARCINOMA
In spite of radical surgical and radiation treatment, the patient, a young adult male, died within six months of metastases of this rare, primary, poorly differentiated adenocarcinoma of the middle ear. X63.

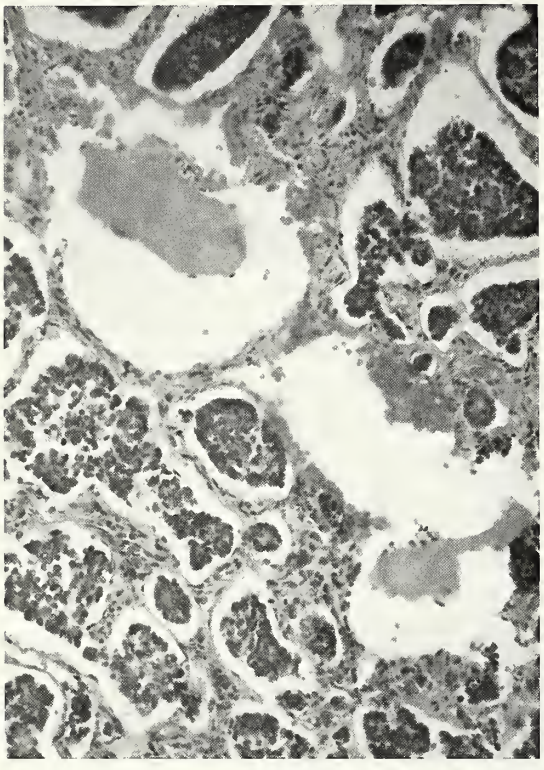

Figure 343
ADENOCARCINOMA X160

space and temporal bone proper. Of interest is a case examined through the courtesy of Dr. John Batsakis, in which an adult female presented with clinical and histologic diagnosis of a middle ear adenoma 10 years previously, but recently had developed a locally destructive temporal bone mass that is histologically consistent with the papillary cystadenocarcinoma.

Clinical. The long clinical course of this papillomatous cystadenocarcinoma presents a confusing constellation of symptoms. The majority of patients mention years of unilateral chronic ear difficulty characterized by drainage and gradual deafness. Three patients gave a history of tumor being removed previously from the affected external auditory canal. Pain was not apparently significant and after years of increasing deafness and inner ear problems, the patients usually developed intracranial symptoms that led to definitive surgery and diagnosis. No patient demonstrated regional or distant metastasis.

Gross. Reports describe mainly a spongy, vascular, cystic mass occupying the middle ear space, with involvement of surrounding bony tissue and possibly with extension into the intracranial and external ear canal.

Microscopic. The basic structure consists of a generally uniform, single layered, cuboidal to columnar cell forming an adenomatous architecture with intermixed small and large cystic spaces lined with prominent papillary projections. The microscopic resemblance to a papillary adenocarcinoma of thyroid can be uncanny (fig. 344) and an initial diagnosis of metastatic thyroid carcinoma may be made. Mitotic activity is not prominent. The cells have a vacuolated cytoplasm with prominent hyperchromatic nuclei. The glandular secretions may have a colloid appearance, even with suggestive scalloping adjacent to the cell borders. The secretions support a positive mucicarmine reaction, although the tumor cells themselves rarely contain mucin. The immunoperoxidase antibody studies against thyroglobulin were negative. The stroma is variable and consists usually of hyalinized connective tissue. The neoplasm and its stroma can be found replacing the osseous tissue of the temporal bone.

Differential Diagnosis. There is the obvious necessity of differentiation from a papillary adenocarcinoma of the thyroid. A negative thyroid workup is helpful. The lack of metastatic involvement of cervical lymph nodes by metastatic thyroid carcinoma should also be of assistance. When the

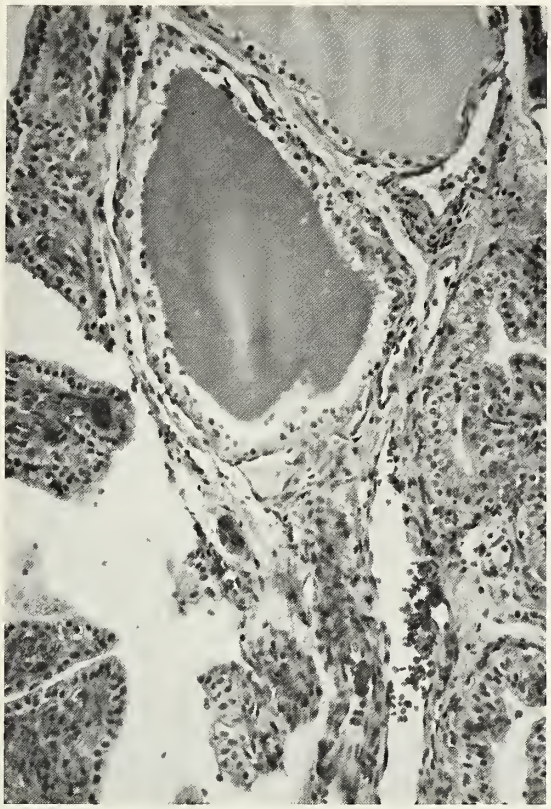

Figure 344
PAPILLARY ADENOCARCINOMA
This magnification shows areas that remind one of the scalloped, follicular pattern of the thyroid. The secretion will have somewhat of a mucin positivity and there will be a negative immunoperoxidase study against thyroglobulin. X160.

cranial cavity is involved, the possibility of confusion with a choroid plexus papilloma or adenoma is present. The limitation of the papillary cystadenocarcinoma of the middle ear to the epidural space, together with its bone destructive properties and mixed papillary and adenomatous cytologic features, should help to delineate it from the choroid tumor.

Treatment and Prognosis. From the slow, local, nonmetastatic aggressive behavior, an aggressive complete surgical removal would seem most appropriate (Schuller et al.). The well differentiated cytology of the neoplasm would discourage irradiation except in a desperate situation. One of the patients died from intracranial extension before surgery, while the remaining seven patients underwent surgical procedures and have survived 2 to 10 years without apparent recurrent disease.

ACOUSTIC NEUROMA

SYNONYMS AND RELATED TERMS: Acoustic neurilemoma; acoustic schwannoma; acoustic neuroma; acoustic neurofibroma; acoustic perineural fibroblastoma.

Definition. Acoustic neuroma is usually a solitary, benign, encapsulated neoplasm originating from the eighth cranial nerve, mainly in its superior vestibular portion. It is composed of Schwann cells proliferating in a collagenous matrix.

Acoustic neuromas account for approximately 8 to 10 percent of all intracranial neoplasms (Schuknecht), and the involvement of the eighth cranial nerve is more frequent than that of all other cranial nerves combined. In the series of 140 patients with acoustic neuromas reported by Erickson and associates, 64 percent were females. Ages ranged from 13 to 72 years, with a mean age of 45 years. Symptoms occurred on an average of 4.3 years prior to treatment. Signs of neurofibromatosis were noted in 16 percent. Bilateral acoustic neuromas were present in 7.8 percent. In the internal auditory canal, the tumor arises almost exclusively from the vestibular portion of the eighth nerve, with rare origin from the cochlear portion or the seventh cranial nerve. Although there is a glial-Schwann sheath junction of the eighth nerve (Rednik-Obersteiner line) immediately inside the meatus of the internal auditory canal, Schuknecht observes that the tumor may arise anywhere between this junction and the cribrosa area at the fundus of the

canal. The progressive growth of an acoustic neuroma of the internal auditory canal produces a sequence of symptoms which tends to occur in the following order: (1) loss of hearing and equilibrium; (2) headaches; (3) cerebellar symptoms; and (4) involvement of adjacent cranial nerves (Schuknecht).

Gross. Acoustic neuromas do not vary from the appearance of schwannomas (neurilemomas) elsewhere in the body in that they are circumscribed masses, usually firm, rubbery, and tan, while the larger tumors may have a yellow discoloration of the cut surface with areas of cystic degeneration, soft edematous foci, prominent vascular spaces, and old or recent hemorrhage. The larger neoplasms usually protrude from the internal auditory canal meatus into the cerebellopontine angle, producing compression of the adjacent brain stem and cerebellum.

Microscopic. The histology of acoustic neuroma is identical to schwannomas (neurilemomas) elsewhere in the body (figs. 345, 346). The diagnostic finding is the delicate, bipolar spindle cells with small, elongated, oval nuclei arranged in a palisading pattern with intervening anuclear areas of eosinophilic stroma, which represent the indefinite cytoplasmic processes of the cells. The whorling pattern of the palisading spindle cells has been designated as Antoni type A pattern, while the Antoni type B pattern is characterized by spindle cells separated by a myxoid or hyaline stroma or sometimes formed only of foamy cells. The proportion of Antoni type A and B histology in any acoustic neuroma will vary but, fortunately, the diagnostic characteristics of the Antoni A are usually present. The tumor can be quite vascular. Schuknecht records a 9 year old girl with malignant degeneration of the acoustic neuroma.

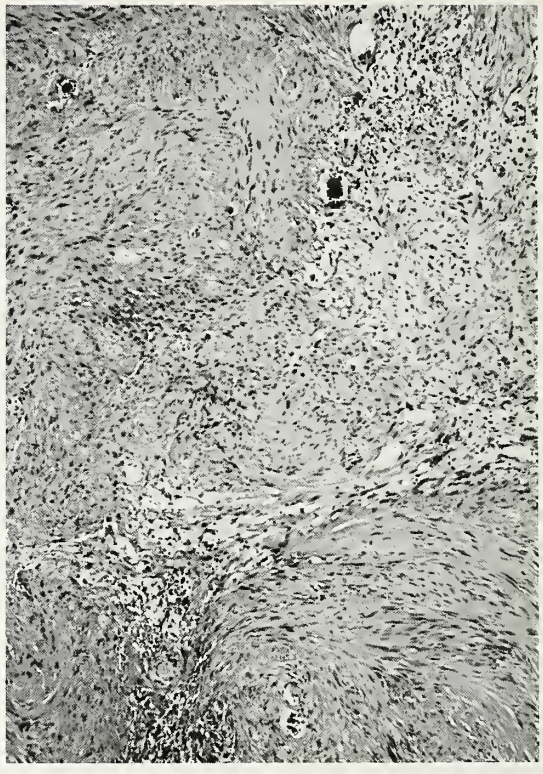

Figure 345
ACOUSTIC NEUROMA
This is the typical histology of neurilemoma, with both Antoni A and B areas, with the major part the former type histology. The Antoni A portions are characterized by nuclear palisading and several areas of Verocay body formation. The Antoni B area is represented in the right lower portion area as the myxomatous area. X63.

A peculiar variant of internal auditory canal tumor has been noted in four cases of temporal bone specimens contained in the AFIP Temporal Bone Repository, one of which was reported by Igarashi and associates. The neoplasms revealed a mixture of areas resembling an acoustic neuroma (neurilemoma) and a psammomatous meningioma (fig. 347). In these four patients, the neoplasms were particularly aggressive, extending into the inner as well as the middle ear and mastoid. The case reported by Igarashi and associates presented with bilateral tumors

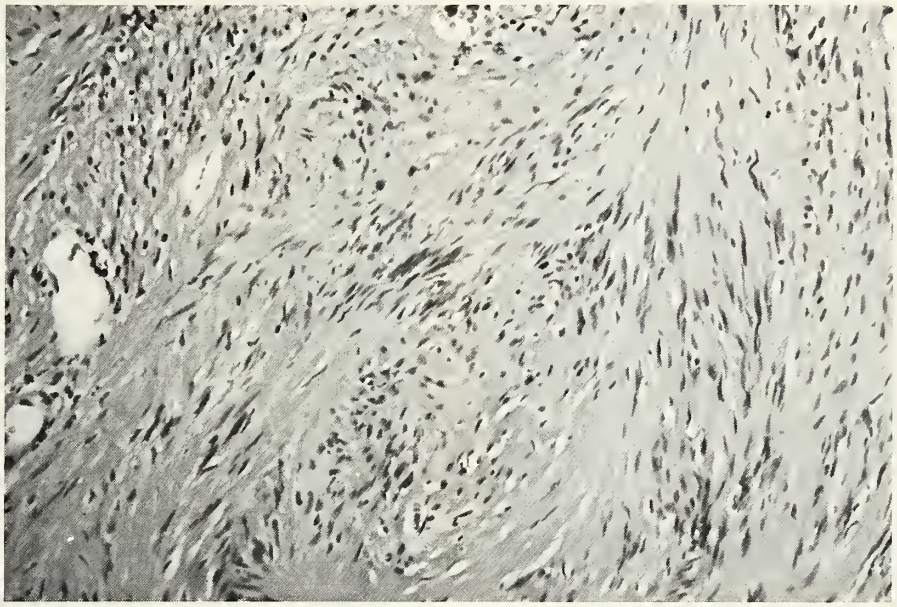

Figure 346
ACOUSTIC NEUROMA
Nuclear palisading and a Verocay body of the Antoni type A areas are shown in the lower portion of the field. X160.

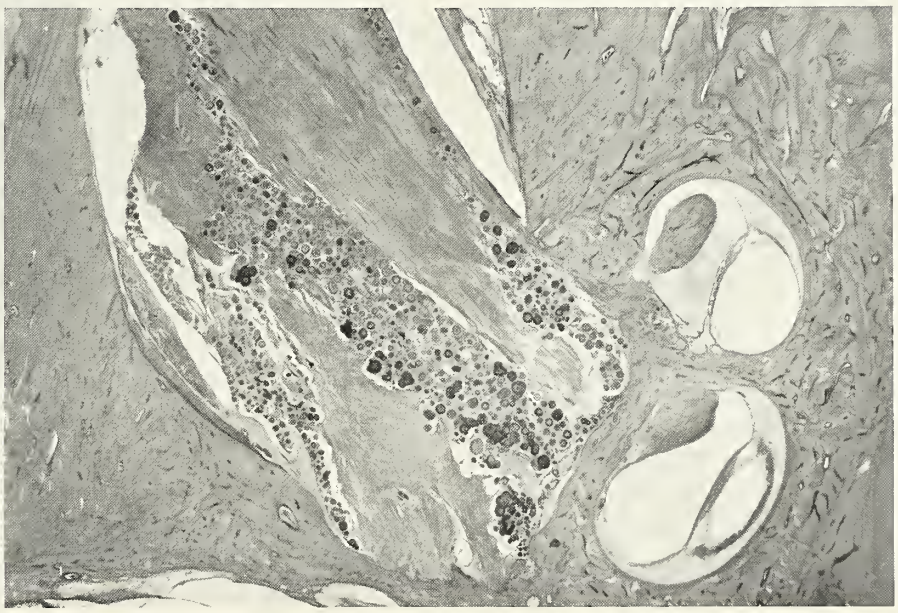

Figure 347
ACOUSTIC NEUROMA
The right horizontal celloidin processed temporal bone reveals a neoplastic infiltrate in the internal auditory canal, representing a mixture of a psammomatous meningioma and a neurilemoma. The neoplasm did infiltrate into the inner and middle ear spaces. X25.

and a history of von Recklinghausen's disease; however, similar information was not available on the three remaining AFIP Repository cases.

Treatment and Prognosis. The only accepted treatment is surgical removal, and survival will depend upon the size of the tumor, operating difficulties, and complications encountered. In the series by Erickson and associates of 123 patients operated upon and followed between 1910 and 1960, 28.4 percent were operative mortalities, and 37.4 percent were felt to present a useful survival.

SQUAMOUS CELL CARCINOMA OF THE MIDDLE EAR

Primary squamous cell carcinoma of the middle ear is a well defined lesion of this anatomic area, and there are 25 patients listed in the AFIP-OTR (Table 25). Etiology appears linked to a long history of chronic otitis media and the occasional case receiving the outmoded irradiation therapy to a middle ear inflammation. There appears to be no link with the presence of cholesteatoma. In the AFIP-OTR material and the 28 patients of Michaels and Wells, there was no sex predilection. The patients ranged in age from the fourth to the ninth decades, with an average age of 60 years.

Clinical. The overwhelming majority of patients will present with a long-standing aural discharge of years' duration. Some will show a blood stained drainage or frank bleeding. Pain in an ear occurs in three-quarters of the patients at the time of diagnosis. A relatively sudden onset of pain in a chronic draining ear is an indication to suspect a squamous cell carcinoma of the middle ear cleft or external auditory canal. Of the 28 patients in the series of Michaels and Wells, all had hearing impairment at diagnosis. Ten patients had facial palsy, 2 had aural swelling, and 1 had vertigo. One patient developed cervical lymph node metastasis nine months prior to death and one other developed clinical lung metastasis just prior to death.

Gross and Microscopic. The observation of Michaels and Wells, following temporal bone examination at autopsy in three patients, suggests that the primary squamous cell carcinoma of the middle ear invades two particular bony areas early in the disease — the thin bony partition separating middle ear and the adjacent eustachian tube from the carotid canal, and the thin bony walls of the posterior group of mastoid air cells. In this way, tumor reaches the sympathetic plexus of the carotid canal and the outer layer of the dura and extensive spread takes place from these locations.

The bony capsule of the labyrinth is resistant to the spread of tumor, but the neoplasm spreads into the internal auditory meatus and may invade the perilabyrinthine bone along the pathway of the nerves supplying the cochlea and vestibule. Spread of the squamous cell carcinoma to the eustachian tube and external auditory canal is common. Six of the 28 patients of Michaels and Wells developed carcinoma in the mastoid cavities. The structure will vary from a well differentiated to poorly differentiated squamous cell carcinoma (figs. 348, 349). Some patients reveal origin of the neoplasm from the cuboidal or columnar epithelium of the middle ear, but, more frequently, a thin surface layer of malignant squamous epithelium forming a portion of the middle ear mucosa appears to give rise to the squamous cell carcinoma. A case of verrucous carcinoma of the middle ear is reported by Woodson and associates. In the differential diagnosis, the experience of the AFIP-OTR material sug-

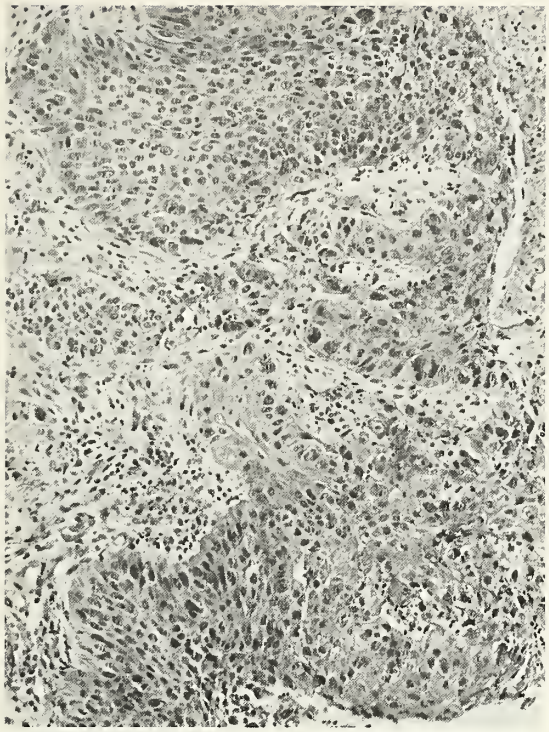

Figure 348
SQUAMOUS CELL CARCINOMA
This histology supports a well differentiated, keratinizing, squamous cell carcinoma of the middle ear space. X63.

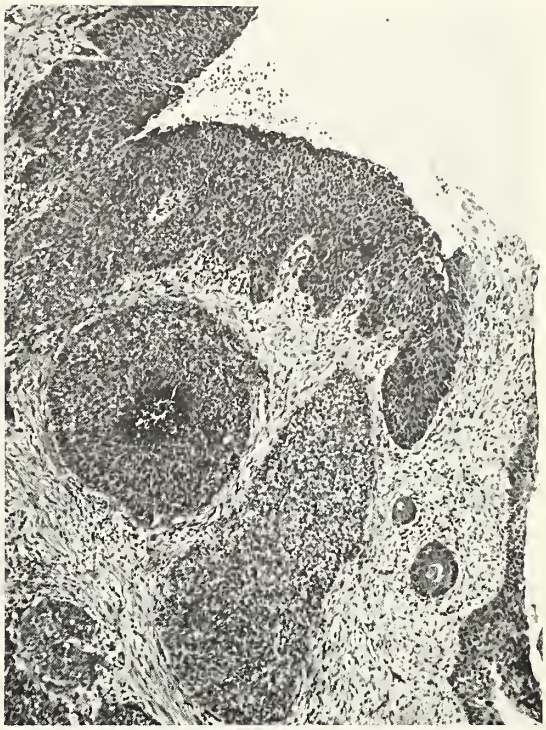

Figure 349
SQUAMOUS CELL CARCINOMA
This malignant neoplasm of the middle ear space represents a poorly differentiated squamous cell carcinoma and supports origin from the middle ear mucosa. X25.

gests that care be made to rule out a metastatic squamous cell carcinoma spreading from the external canal and the nasopharynx, the latter via the eustachian tube. Microscopically, the pathologist must guard against underdiagnosing the well differentiated squamous cell carcinoma as a cholesteatoma.

Treatment and Prognosis. Radical surgery together with irradiation therapy is the most common therapeutic approach. Chemotherapy also has been incorporated. In the series of Michaels and Wells, the 5- and 10-year survival was 39 percent and 21 percent, respectively. In a survey of several series in the English medical literature of middle ear squamous cell carcinomas that were treated with surgery or irradiation alone or in combination, the five-year survival rate was from 20 to 30 percent. The prognosis with squamous cell carcinoma of the middle ear may be improved by having a high level of suspicion of this disease when assessing each patient with a discharging ear.

MELANOMA

There are two patients with melanoma of the middle ear listed in the AFIP-OTR, but there is not enough confidence in this diagnosis that one can rule out the possibility of metastasis from an unidentified distal primary site. The identification of melanin bearing

cells in the normal middle ear mucosal area has not been accomplished in the AFIP Temporal Bone Repository material; however, Babin and Benjamin published a case of a primary blue nevus in the middle ear of a 28 year old patient. There are quite a few melanin bearing cells seen in the normal modiolus of the inner ear, but as yet no definite proven neoplasms from this anatomic area have been identified.

ADDITIONAL NEOPLASIA OF THE MIDDLE EAR AND INNER TEMPORAL BONE AREA

From the information gained in Table 25, there are numerous other neoplastic entities listed as primary in the middle ear and inner temporal bone anatomic areas. These are more of mesenchymal derivation, particularly bone. Some of these additional neoplastic entities will be discussed in other sections of this and other Fascicles and others are of such low incidence that the reader is referred to other texts and the literature for further discussion.

The internal auditory canal is the site of mainly acoustic neurilemomas and occasional meningioma, neurofibroma, or cholesteatoma. Olson and associates, however, have presented two cases of lipomas of internal auditory canal, as well as a discussion of additional cases of lipomas and other lesser known neoplasms of the internal auditory canal. There are several cases contained in the AFIP-OTR of histologically benign vascular neoplasms listed as arising from the internal auditory canal. The symptomatology of these rare tumor entities in this anatomic area did lead to a clinical presentation suggestive of an acoustic neuroma.

METASTATIC NEOPLASIA TO THE TEMPORAL BONE

Metastatic neoplasia of the temporal bone is probably more frequent than the literature would suggest, because of the lack of attention to the temporal bone area by the clinician and autopsy pathologists in cases of disseminated cancer. However, metastatic tumors may often mimic primary temporal bone neoplasia as well as nonneoplastic disease. It is always wise to rule out as far as possible any distant primary adenocarcinoma when such a tumor appears to involve the middle ear or temporal bone. A percentage of these tumors metastatic to the middle ear probably represent direct extension from adjacent areas (pharynx, intracranial space, salivary gland, and cervical lymph nodes). Schuknecht and associates reported on 73 cases from the literature. In their experience with secondary malignant tumors involving

Table 29

METASTATIC NEOPLASIA TO TEMPORAL BONES FROM DISTANT PRIMARIES*

Primary Site and/or Neoplastic Classification	No. Cases
Breast carcinoma	18
Lung carcinoma	12
Renal adenocarcinoma (hypernephroma)	10
Stomach carcinoma	8
Larynx carcinoma	5
Melanoma	5
Prostatic adenocarcinoma	4
Thyroid carcinoma	4
Pharyngeal carcinoma	4
Cervix and uterus carcinoma	4
Neoplasia — miscellaneous	29

*Adapted from Hill, B.A. and Kohut, R.I.

the temporal bone, the descending order of primary site frequency was breast, kidney, lung, stomach, prostate, and thyroid (see Table 29 of Hill and Kohut). Since the metastases are felt to be mainly hematogenous, the marrow spaces of the temporal bone are suggested as areas of stasis of the disseminating tumor cells. The involvement of the peculiar enchondral bone of the osseous labyrinth (inner ear) by metastatic tumor is rare; however, Oshiro and Perlman added 5 patients of their own to 10 previously reported in the literature that showed direct extension of metastatic disease of the subarachnoid space into the inner ear through the eighth nerve pathways.

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